Section of Radiology

President Frank Ellis MD

Meeting October 21 1960

Paper

A O Kovalevski and the Neurenteric Canal: A Note on Some Historical Inaccuracies

by Edward B D Neuhauser MD and
Herbert J Kaufmann MD (*Boston, Mass., U.S.A.*)

In a recent paper J R Smith [21] has attempted, because of a 'considerable confusion in the present classification and nomenclature of accessory enteric formations', to provide a practical classification founded on the basic embryological deviations. This effort has been to a great extent successful but there is still confusion as to the nature of the deviation. Dorsal enteric remnants, including fistula, sinus, cyst, duplication, diastematomyelia, and the characteristic abnormality of the vertebra have been attributed to remnants of the neurenteric canal or accessory canals, or to a split notochord [1, 22–24].

Eponyms may have their merit but at the same time can present certain pitfalls. Recently one of us [1] in presenting a paper on malformations related to a persisting neurenteric canal of Kovalevski, concluded that there was confusion over the identity of the man to whom the discovery of this embryonic structure is ascribed. The feeling arose that he might be virtually lost to posterity due to some unknown or unapparent twists of fate. The reason becomes immediately evident when we relate the information that can be obtained from the standard medical encyclopedias and other reference works usually consulted in such a predicament. No direct reference to Kovalevski's original description is contained in the recent and accessible medical literature or in the current embryology texts.

The student of Kovalevski's canal turning to the listed works is informed on the identity of Kovalevski in the manner shown in Table 1.

Not one of the captions below is completely correct. The name of the man we are tracking down correctly reads 'Alexander Onoufrievich Kovalevski'. He was not an anatomist but an outstanding embryologist, who lived from 1840 to 1901. It is interesting to see what happened to the discoveries and writings of the Russian scientist.[1]

[1]Access to the writings of A O Kovalevski was possible through the Royal Society Catalogue of Scientific Papers Vol. 8 (1864–73) and Vol. 10 (1874–83) [2]

Table 1

1935	Gould's Medical Dictionary, 4th ed., Philadelphia	Pavel Ivanovich Kovalevski Russian embryologist 1845–
1941	Dorland's Illustrated Medical Dictionary, 19th ed., Philadelphia & London	Pavel Ivanovich Kovalevski Russian anatomist 1845–
1946	Stedman's Medical Dictionary, 16th ed., Baltimore	Pavel Ivanovich Kovalevski Russian embryologist 1845–
1948	E C Kelly: Encyclopedia of Medical Sources, Baltimore	Not mentioned
1949	H A Skinner: The Origin of Medical Terms, Baltimore	Not mentioned
1953	C Wakeley: The Faber Medical Dictionary, London	Kovalevski P Russian embryologist 1845–1901
1956	Blakiston's New Gould Medical Dictionary, 2nd ed., New York, &c.	Not mentioned
1957	Stedman's Medical Dictionary, 19th ed., Baltimore	Nikolas Opsipovich Kowalewsky Russian physiologist and histologist 1840–189?
1957	Dorland's Illustrated Medical Dictionary, 23rd ed., Philadelphia & London	Alexander Onoufriev. :h Kovalevski Russian anatomist 1846–1901

Let the historical record speak for itself. In a communication entitled 'Weitere Studien über die Entwickelungsgeschichte des Amphioxus lanceolatus, nebst einem Beitrage zur Homologie des Nervensystems der Würmer und Wirbelthiere' Kovalevski [3] states

'I have recognized the contiguity of the posterior segments of the intestinal and neural tubes; i.e. their direct continuation into one another in Acanthias in 1867. This was published and documented in the year 1869. In Acanthias the embryonic plate represents a true plano-gastrula [4].

'The two embryonic leaves – superior and inferior intestinal glandular leaves – are contiguous at the borders of the embryonic plate. The primitive groove forms at these borders of the embryonic plate and extends from above to below the embryonic plate. At the time of closure of the groove, the superior portions form the medullary tube and the inferior portion mainly the posterior end of the intestinal tube. The contiguity of these two tubes in Acanthias persists up to the time of formation of the anus, then it disappears.

'This description was neglected by most workers in the embryology of Plagiostoma and in particular with reference to the special point of the communication between the posterior ends of the intestinal and neural canals. Thus, quite unjustly, Balfour ascribes this discovery to himself. Besides in the already mentioned paper in Russian, I have given reference to this point in further communications with regard to Acipenseridæ and Axolotl [5, 6]. It thus should have been easy for Balfour to learn whom the original description is due to. I shall not mention Semper who also had my paper on the Development of Acanthias in his hands, since that article appeared in Russian.'[1]

'*Easy Methods to Rediscover the Already Known*'

Balfour himself quotes Kovalevski frequently and in his 'Treatise on Comparative Embryology' [9] in 1885 remarks, in a footnote, 'There is a striking similarity between the history of the neurenteric canal in vertebrates and the history of blastopore and ventral grooves as described by Kovalevski in the larva Chiton'.

From all the evidence it appears incontestable that the original description of the neurenteric canal should be ascribed to Kovalevski. We found it rather difficult to establish to whom the merit should be given of assuring his name a nook of immortality in the list of medical eponyms. The earliest reference to A O Kovalevski we could find, within the context under discussion here, is in Charles Sedgwick Minot's 'Human Embryology' published in 1892 [7]. Minot (1852–1914) was Professor of Histology and 'Human Embryology' at Harvard Medical School. Under the heading 'Neurenteric Canal' Minot diplomatically states, 'We owe to Balfour the identification of this canal as the blastopore. It may with propriety be termed the true neurenteric canal, or the canal of Kovalevski from its discoverer. Kovalevski first found it in Amphioxus and subsequently demonstrated its occurrence in various fish types'. However, Minot does not include any reference to the work of Kovalevski in this text or in his 'Bibliography of Vertebrate Embryology' published in 1893 [8]. There we find eleven references to the neurenteric canal, but no mention of Kovalevski (Refs. 1773 to 1783).

Fig 1 *Alexander Onoufrievich Kovalevski* [17]

It is of historical interest that on page 191 Minot [7] writes, 'It seems not impossible that a persistent neurenteric canal may occur as an excessively rare anomaly in the adult'.

The only biographical note of Kovalevski we could find in English is the obituary by E R Lankester [10]. Biographic notes compiled with the help of the famous scientist Metchnikoff of the Institut Pasteur in Paris convey a good picture of Kovalevski's background and achievements. Besides information on his training, in great part obtained in Heidelberg and Tübingen, there are good data on his work in research (Naples, 1864, and Naples and Ischia, 1866) and as an academic teacher (Kazan, Kiew, Odessa and St Petersburg). Amongst many other honours bestowed upon him he was made a Foreign Member of the Royal Society.

[1]Semper: Stammesverwandtschaft der Wirbelthiere und Wirbellosen, p 15. 'Unfortunately, I cannot cite Kovalevski's paper since it is written in Russian.'

A short personal note by Lankester may be quoted here. 'Personally, Kovalevski was a man of retiring disposition, devoted to his microscopic work and of the most gentle and courteous address. He visited England with one of his daughters in October 1895 for a few days but took alarm at the dangers of the London streets and left somewhat abruptly.'

A O Kovalevski is referred to as 'an academician of St Petersburg (1844 to 1901) and an important representative of philogenetical embryology' in Nordenskjöld's 'History of Biology' [11]. The best appraisal of his importance can be gained in Locy's 'Biology and its Makers' [12]:

'Kovalevski made interesting discoveries of a general dealing. In 1866, he showed the practical identity, in the early stages of development, between one of the lowest vertebrates (Amphioxus) and a Tunicate. The latter up to that time had been considered an invertebrate, and the effect of Kovalevski's observations was to break down the sharply limited line supposed to exist between the invertebrates and the vertebrates. This was of great influence in subsequent work. Kovalevski also founded the generalization that all animals in development pass through a gastrula stage – a doctrine associated, since 1874, with the name of Haeckel under the title of "Gastraea Theory".'

The modern Russian scientists have not forgotten this pioneer of embryology. Ivanov [13] assesses the impact of his contributions at the occasion of his 100th anniversary. His objective appraisal leads up to the conclusion that 'the truly major and scientific attainments stand beyond the law of historical perspective and, therefore, everything that has been accomplished by A O Kovalevski towards the establishment of the general concept of embryology, towards the elucidation of the complex characteristics of the individual species of animals and finally towards the establishment of the principle of evolution, remain clearly and unchanged as his contribution and achievements and will as such remain in our memories'.[1] On the same occasion appeared a paper by Knorre [14], 'A O Kovalevski, the Founder of Comparative Embryology', together with biographical notes by Nekrasov [15]. Lastly, Dogel [16] wrote a book on Kovalevski which we have been unable to obtain.

As the name of Pavel Ivanovich Kovalevski has for so long mistakenly been connected with the neurenteric canal, we would like to add that he was a great physician in his own right [18]. He was born in 1845. The date of his death cannot be established. He was an outstanding neurologist and psychiatrist and published widely. One of his works was translated into French and served as a textbook under the title 'Legal Psychopathology' [19]. His psychiatric historical sketches (1892-93) of Ivan the Terrible; Ludwig II, King of Bavaria; Nebuchadnezzar, King of Babylon; Saul, King of the Jews; and Cambyses, King of Persia are still quoted.

Finally, we must mention the third Kovalevski who lived at the same period and whose name has added to the confusion (*see* Stedman's Medical Dictionary, 19th ed., Baltimore, 1957). Nikolas Opsipovich (von) Kowalewsky [20] (1840–1892) was Professor of Physiology at the University of Kasan and published many basic contributions in his field.

We trust that this brief note will end the confusion created by the omissions and errors of the past. Each of these scientists deserves his own niche in medical history.

[1]For the kind help in the translation of the original Russian sources we express our gratitude and indebtedness to Dr L Snegireff

REFERENCES

1 **Neuhauser E B D, Harris G B C & Berrett H A** (1958) *Amer. J. Roentgenol.* **79**, 235
2 **Royal Society of London** (1879, 1894) Catalogue of Scientific Papers. London; 1864–1873, **8**, 116, ref. 3–16; 1874–1883, **10**, 450, ref. 17–26
3 **Kovalevski A O** (1877) *Arch. mikr. Anat.* **13**, 181
4 **Kovalevski A O** (1869) Schriften der Naturforschergesellschaft in Kiew. Kiew; **1**, 163
5 **Kovalevski A O** (1871) *Arch. mikr. Anat.* **7**, 101
6 **Kovalevski A O, Ovsjannikov P H, & Wagner N** (1869) *Bull. Acad. Sci. St-Pétersb.* **7**, 176
7 **Minot C S** (1892) Human Embryology. New York
8 **Minot C S** (1893) *Mem. Boston Soc. nat. Hist.* **4**, 540, ref. 1773–1783
9 **Balfour F M** (1885) A Treatise on Comparative Embryology. London.
10 **Lankester E R** (1902) *Nature, Lond.* **66**, 394
11 **Nordenskjöld E** (1929) The History of Biology. Trans. L B Eyre. New York & London
12 **Locy W A** (1930) Biology and its Makers. 3rd ed. New York; p 224
13 **Ivanov P P** (1940) *Bull. Acad. Sci. U.R.S.S.* sér. biol., p 819
14 **Knorre A G** (1940) *Usp. Sourem. Biol.* **13**, 195
15 **Nekrasov A D** (1940) *Usp. Sourem. Biol.* **13**, 195
16 **Dogel V A** (1945) A O Kovalevski. Moscow
17 Portrait Catalogue of the Library of the New York Academy of Medicine. Boston; **3**, 2201
18 Kovalevski P I: Index Catalogue of the Library of the Surgeon General's Office, 1st & 2nd ser.
19 **Kovalevski P I** (1903) Psychopathologie Légale. Paris.
20 **Kovalevski N O** (1929–35) Biographisches Lexikon hervorragender Ärzte aller Zeiten und Völker. 2nd ed. Berlin-Wien
21 **Smith J R** (1960) *Arch. Dis. Childh.* **35**, 87
22 **Cohen J & Sledge C S** (1960) *Amer. J. Dis. Child.* **100**, 257
23 **Bremer J L** (1952) *Arch. Path., Chicago* **54**, 132
24 **Bentley J F R & Smith J R** (1960) *Arch. Dis. Childh.* **35**, 76

Meeting February 17 1961

Papers

Physiological Concepts of the Pylorus[1]

by D A W Edwards MD MRCP (*London*)

This paper concerns the physiological behaviour of the segment of muscle between the body of the stomach and the duodenum. This segment includes the pyloric antrum and the pyloric ring or valve but cannot be accurately defined because there is no precise proximal anatomical limit; the distal limit is the beginning of the cavity of the duodenal cap.

Part of this muscle is sometimes called the pyloric sphincter. The definition of a sphincter given in the Concise Oxford Dictionary is 'a muscle surrounding and serving to close an opening'. Because of the way our anal and urethral sphincters work we are sometimes inclined to have a special interpretation of this word which influences our idea of the action of the pylorus. We think of a muscle band that closes an opening and keeps it closed, occasionally relaxing to let something through. Although the cricopharyngeal and cardiac sphincters behave in this expected fashion, the pylorus does not.

The behaviour of a sphincter can be demonstrated by manometry. The aim is to measure the pressure in the lumen of the gut and demonstrate a zone where the force imposed by the wall is greater and so closes off this segment from the rest of the gut tube. This can be done either with an open-ended tube or a miniature balloon. The open tube will not record any excess pressure in the zone as long as the fluid contents can flow freely along the segment into the gut at either end (Edwards & Rowlands 1960). On the other hand, if the segment is squeezed tight, a rise of pressure may be recorded with the open tube which will measure the squeezing force. The miniature balloon records a different property of the muscle wall, namely its resistance to being stretched by the balloon. These two methods give us a way of measuring both the positive squeezing power of a muscle structure and its power of remaining in a particular shape without actively compressing the contents of the lumen, which is a measure of the rigidity or plasticity of the muscle.

The method used is to pass the recording tips of the tubes beyond the segment of gut to be studied, and then to withdraw the tips in 1 cm steps, recording the resting pressures and the changes produced by activity of the segment at each step.

The cricopharyngeal sphincter is an example of a striated muscle sphincter which is closed all the time except during a swallow, when the continuous shower of impulses from the brain-stem stops and the muscle relaxes to allow the bolus to be pushed through by the contraction of the pharyngeal constrictors. Andrew (1956) has demonstrated the interruption of the motor impulses to the muscle in the rat, and Doty & Bosma (1956) have recorded electromyogram potentials from the various muscles involved in swallowing in the dog, illustrating how the high resting tone of the sphincter relaxes at the right moment as part of the complicated reflex process of swallowing.

The pressure record from the cricopharyngeal sphincter in man shows a high resting pressure of about 40 cm water with an open tube (Fyke & Code 1955) which falls for about 0·5 sec to the intra-œsophageal pressure during a swallow, rising again with an overshoot. The cardiac sphincter is a plain muscle structure which behaves in a similar way except that the time relations are about ten times slower. As the tip of the recording tube is drawn up from the stomach the resting pressure with an open tube rises to an average of 3 cm water above the fundus pressure for a distance of 2–4 cm, recording the positive squeeze of the muscle segment. A 3 mm diameter balloon, 10 mm long, also records a high resting pressure in the same region, averaging 10 cm water, and records the resistance of the wall of the segment to being distended to 3 mm bore. Both the open tube and balloon high resting pressures fall to the surrounding basal pressure about 1·5–2 sec after the pharyngeal phase of swallowing, remain low for a few seconds, and rise again with an overshoot as the peristaltic wave moving down the œsophagus reaches the sphincter (Atkinson *et al.* 1957).

The essential features of these two sphincters are that: (1) They are formed by a segment of the wall of the gut tube, which has a separate innervation. (2) The muscle is tonically contracted, keeping the lumen tightly closed. (3) This tonic contraction relaxes for a short and definite period of time to allow a bolus to be pushed through.

In 1956 the same method of study was applied to the pylorus (Atkinson *et al.* 1957) and in 1959 the experiments were repeated with Dr K Skyring. An open tube was pulled through the pyloric seg-

[1]Work undertaken on behalf of the Medical Research Council

ment from the duodenum a total of twenty-nine times in 18 fasting normal subjects and seven times in 5 normal subjects with a full stomach, but on no occasion was any evidence found of a segment with a sustained rise of squeeze pressure like that found in the cricopharyngeal and cardiac sphincters.

It seemed possible, although unlikely, that the pyloric segment was so short that an open tube or a single miniature balloon might slip through and simply record a short blip on the tracing. To overcome this possibility we used a chain of four 7 mm diameter balloons, recording synchronously, which were arranged in such a way that there was no part along a 5 cm long cylinder that could not record a laterally applied force. This balloon chain was pulled through the pyloric segment in 1 or 2 cm steps so that at some stage the chain must have straddled the pylorus. Although this cylinder was pulled through twelve times in 7 normal fasting subjects and seven times in 6 normal subjects with a full stomach, again no segment with a sustained resting pressure, due either to squeeze or to resistance to stretch, could be demonstrated. Under the conditions of this experiment the pyloric segment did not significantly resist being distended to a bore of at least 7 mm most of the time, and was clearly not a tonically contracted muscular ring, keeping the lumen tightly closed.

Dr Skyring and I carried out a second series of experiments in 1959 with larger balloons of 10, 12, 15 and 20 mm diameter in an attempt to measure the bore of the pyloric channel and its capacity to be distended without resisting. The balloons were passed into the duodenum in 4 subjects, inflated with a measured volume of air, and drawn back in short steps in a total of 8 series of withdrawals.

The 10 mm balloon occasionally produced a rise of pressure, the 12, 15 and 20 mm more frequently. On some occasions it was not possible to pull the 15 and 20 mm balloons through from the duodenal cap and the balloons were deflated before they could be withdrawn. On one occasion the 10, 12 and 15 mm balloons recorded a rise of pressure as they came through the pyloric segment, indicating that the wall was resisting their distending force, but a few moments later the 20 mm diameter balloon slipped through without a rise of pressure, showing that the muscle had relaxed again. These two series of experiments suggested that, in the conditions of the experiment, the pyloric channel, most of the time, offers little or no resistance to being stretched to 7–12 mm diameter or even occasionally up to at least 20 mm diameter.

The emphasis is on *most of the time*. The pylorus closes firmly at times. In the experiments in which a cylinder of four balloons was pulled through the pylorus, the pyloric region itself could be identified on the tracings because the tracing from the duodenal cap is characterized by bursts of short based spikes, and the tracing from the pyloric antrum by broad based pyramids occurring three times a minute. About every 60–90 sec a giant wave, 50–100 cm water high, lasting about 5 sec, appeared in all four tracings simultaneously, involving the pyloric antrum, the pyloric segment, and the proximal part of the duodenal cap. This type of activity appears in bursts during much of the time of recording from the pyloric channel, but the frequency of the bursts over periods of an hour or more has not been determined, nor is it known whether the behaviour of the segment is influenced by the presence of the recording tube. These waves must squeeze the antrum-pylorus-duodenal cap segment approximately simultaneously, and in doing so would force the contents of the segment out in both directions, back into the stomach and forward into the duodenum.

Discussion

It seems possible that this rhythmic contraction might have a pump-like action, filling in diastole from the stomach and emptying in systole in both directions, squirting the contents of the segment, with at best a 50% efficiency, into the duodenum. The basal pressure in the stomach and duodenum is determined largely by the hydrostatic pressure due to overlying viscera and in pressure records is constant over long periods of time so that there is no gradient of basal pressure between the stomach and the duodenum. Filling of the pump in diastole from the stomach may therefore depend upon gravity or phasic changes in antral pressure. The duodenal lumen is continually subjected to phasic changes of pressure, produced by contraction of its wall, which are propulsive and which can be demonstrated by manometry, or their effects seen at fluoroscopy. Occasional bursts of retroperistaltic activity can be shown by these methods but most of the time the duodenum empties itself rapidly in a forward direction, acting as a continuously moving conveyor belt, and it is this action which is most likely to form a non-return valve for the pyloric segment pump.

For these reasons the following concept of the pyloric segment is suggested: the pylorus is a thick-walled connecting piece between the stomach or hopper and the small intestine or conveyor belt, which acts in two distinct ways: (1) It acts *statically* as a filter by virtue of the relative narrowness of its bore, holding back lumps of food, but capable of varying its bore

from nothing to 20 mm or more like a long iris diaphragm. (2) It acts *dynamically* as a pumping machine which provides one of the important motive powers for emptying the stomach. It does not therefore prevent gastric emptying by acting as a sphincter in the way that the cricopharyngeal and cardiac sphincters work, but promotes gastric emptying by acting as a pump.

How can these experimental findings be reconciled with the radiological appearance of the pylorus? There are some points of agreement; the fluoroscopic appearance of the behaviour of the pylorus is quite different from that of the cricopharyngeal and cardiac sphincters; barium does flow through the pylorus most of the time; and the barium column can be seen to vary its width from nothing to a wide channel. The main points of difference seem to be first, that the pyloric shadow appears narrow or obliterated more often than might be expected from the pressure tracings; secondly, that movement of the shadow occurs giving the appearance of barium being pushed by a gastric peristaltic wave against a closed pylorus, or the pyloric antrum appears to balloon out proximal to a constriction; and thirdly that barium sometimes flows into the duodenum without detectable pumping action of the pylorus, and will do so after a pylorectomy. The following discussion is an attempt to find a way out of these difficulties and explain the radiological appearances.

The pyloric segment has an inner circular layer of fibres, and an outer longitudinal. The circular fibres are increased in number and commonly bunched up to produce a thickening of the wall of the segment about 2 cm along the lesser curve side and about 4–5 cm along the greater curve. Formalin and rigor mortis make these fibres contract giving the familiar dissecting-room and pathology-pot appearance of a well-defined thick ring of muscle, but sometimes at laparotomy or at autopsy it may be difficult to distinguish any local thickening, and the pyloric region must be identified by the pyloric vein. Some of the longitudinal fibres continue into the duodenum, but the deeper layers are turned inwards to be inserted into the circular layer in the region of the pyloric ring. When the circular fibres contract the lumen will be narrowed, and when the longitudinal fibres contract the muscle will be bunched and the lumen encroached upon. It is possible that those longitudinal fibres which are inserted into the circular fibres at the pyloric ring may be able to open the ring, but they could only do so by contracting against the resistance to compression of a distended pyloric antrum as though they were pulling round a pulley wheel. The important point is that there is otherwise no active process which will pull open the lumen of the pyloric segment or the duodenal cap; the lumen can be widened only by an adequate pushing force from within the lumen. After active contraction with change in shape the muscle may remain fixed, resisting any attempt to stretch it, behaving like a rigid structure; or it may relax its tone, giving way to any pressure which can overcome the viscosity of the muscle, exhibiting plasticity again. The important feature of this mass of muscle seen at fluoroscopy is that it is a relatively formless, writhing, fluid mass, constantly varying its shape, relaxing and contracting in all directions, behaving in a manner quite different from that of the cardiac sphincter.

This property of writhing contraction with alternate rigidity and plasticity may explain the first point of difference, the frequency with which the barium shadow is narrowed or nipped off. Fluoroscopy shows the shadow changing its shape, but does not measure the forces involved in this process. Very little force may be required to change the shape of a bag of fluid, so little that if a miniature balloon opposed it, there would be no detectable rise of pressure. A study of ciné-radiographs of barium moving in the pyloric region with simultaneous recording of pressure from a chain of balloons in the area has demonstrated this on four occasions. There may, therefore, be a narrowing of the barium shadow, but this does not necessarily mean a change of intraluminal pressure, nor does it necessarily mean that the muscle is exerting a powerful force either in promoting or obstructing the flow of barium. The second point in this connexion is that once the pyloric segment has been narrowed down by a positive contraction, the barium shadow will retain this shape until there is a pushing force from within the lumen which will broaden the shadow, or until the muscle is pulled into another shape. The discrepancy between the appearance of the barium shadow and the pressure record may be resolved in this way.

This point leads to the second and third difficulties, the failure of the shadow at the pylorus to move in the face of apparent forces, and the converse, the movement of barium from the stomach into the duodenum without any visible pumping action of the pyloric segment. The key to the understanding of these paradoxes is that flow requires a pressure gradient, but absence of flow may be the result of either a resistance to flow greater than the propulsive force, or simply a lack of a propulsive force.

Several forces might propel barium from the stomach or act to distend the lumen of the pyloric segment.

(1) *Gravity:* The amount of the gravitational force will be proportional to the height of the barium column and the difference between the specific gravity of the barium suspension and that of the surrounding tissues. The barium commonly used has a specific gravity of 1·2 and the abdominal viscera of 1·06. Theoretically a column of barium 10 cm high, in the abdominal cavity, will exert a differential pressure of $10\times(1{\cdot}20-1{\cdot}06)=1{\cdot}4$ cm water. The driving force of gravity is therefore often very small, but if the resistance to flow into the duodenum is negligible, because the duodenal wall is relaxed, this small force will be adequate to cause flow of barium. On the other hand, if the lumen is closed with a resistance to stretch of only 2 cm water pressure, this will be adequate to stop flow, but will not be detected with certainty on a pressure record.

(2) *The propulsive activity of the stomach:* The so-called peristaltic activity of the stomach, the deep-cutting waves which move down from the fundus, rarely if ever push barium forwards. During violent activity seen by fluoroscopy there may be no change in pressure in different parts of the stomach until the muscle is contracted down to a tight ring, completely occluding the lumen. This occlusion is a rare event except in the pyloric antrum, and the effect of the deep cutting waves is to agitate and mix the contents of the stomach but not to propel them.

(3) *The pyloric pump:* The pyloric antrum contracts about three times a minute, producing a rise of pressure in a miniature balloon. Every fourth, fifth or sixth wave is accompanied by a simultaneous contraction of the proximal part of the duodenal cap and the pyloric ring, forming the pyloric pump previously described. These waves seem to form the main propulsive activity of the stomach although they are clearly not essential to emptying since the stomach empties at approximately the same rate after a pylorectomy.

(4) *The duodenal or small intestine pump:* This process removes barium or food from the stomach by acting as a continually moving conveyor belt and is not, strictly speaking, a force propelling barium from the stomach. It is probably important after a Billroth I or Polya partial gastrectomy and after gastroenterostomy. It is only necessary for gastric contents to seep into the small intestine lumen for them to be carried away, and little or no gradient of pressure is required to feed the conveyor belt. The probable importance of this conveyor belt mechanism is illustrated by the marked delay in gastric emptying which occurs in systemic sclerosis when the plain muscle of the duodenum and small intestine is atrophic so that this part of the gut becomes immobile, although the stomach itself remains active.

These are the forces which may be involved in promoting emptying of the stomach. Resistance to flow may be produced by resistance to stretch of the pyloric segment or pyloric ring, or by the duodenal cap or beyond. The forces involved may be only a few cm of water pressure, but they may be adequate to withstand the propelling forces.

Acknowledgments: I am very much indebted to my colleagues Drs M Atkinson, E N Rowlands, K Skyring and Mr A J Honour with whom the experimental work was carried out; and to Mr R W Larkin of the London Rubber Co. who provided the miniature balloons.

REFERENCES

Andrew B L (1956) *J. Physiol.* **134, 729**
Atkinson M, Edwards D A W, Honour A J & Rowlands E N (1957) *Lancet* **ii, 918**
Doty R W & Bosma J F (1956) *J. Neurophysiol.* **19, 44**
Edwards D A W & Rowlands E N (1960) Medical Electronics. Ed. C N Smyth. London
Fyke F E & Code C F (1955) *Gastroenterology* **29, 24**

Some Radiological Aspects of Pyloric Disease

by David Edwards MRCP FFR (*London*)

The stomach was subdivided into four parts on a histological basis by Aschoff in 1923. He named the zones the cardia, the body, the vestibule and the pylorus. The term vestibule is not now frequently used and has largely been replaced by the anatomical term the pars pylorica or the pyloric antrum. In such an easily distensible organ as the stomach these subdivisions do not form well-marked anatomical entities but it is generally accepted that the pyloric antrum represents that portion of the stomach which lies distal to the incisura; this only approximately defines that region of the mucosa containing the pyloric glands. Its size and shape varies greatly with the patient's build and the degree of distension of the stomach. Distally the pyloric antrum narrows down to form the pyloric ring, a passage of uniform diameter with a sharply defined termination in the base of the duodenal cap. An attempt was made to define the length of the normal pyloric ring by examining 70 consecutive, normal barium meals in which the limits of the ring appeared to be sharply defined. The mean length of the ring was 6·7 mm with normal limits of 1·0 to 12·0 mm. Any pyloric ring which exceeds 12 mm in length should be carefully examined with grave suspicion.

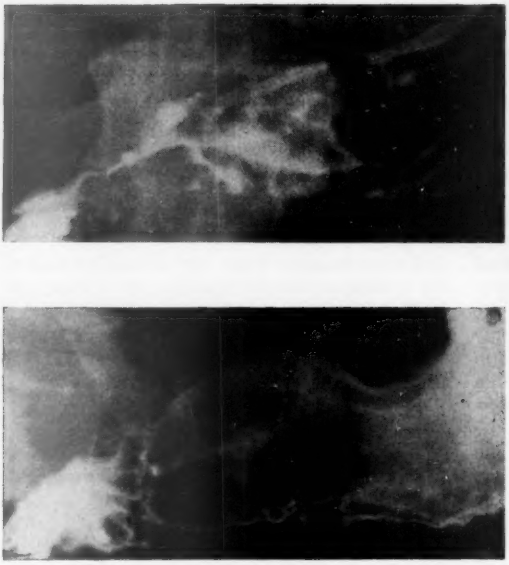


Fig 1A and B *Abnormal mucosal pattern produced by gastric carcinoma almost completely obliterated by distension of the pyloric antrum*

Fig 2 *Lymphosarcoma of the pylorus*

The pylorus is a notoriously difficult region to examine radiologically but the problem is made considerably easier if adequate mucosal relief films are obtained. Shanks (1950) quoted Berg as saying 'The less barium you give the more you see'. This has long been recognized but is surprisingly often neglected. The erect first mouthful film is of little value. Far better films are obtained if, after swallowing one fluid ounce of undiluted Micropaque, the patient is tilted into the supine position and films obtained following the Hampton manœuvre. In this manner both the anterior and posterior walls of the stomach are coated with barium and the likelihood of a lesion on one wall being obscured by a normal mucosal pattern on the opposite wall is much reduced.

A double contrast film of the pyloric region should also be obtained when the patient has swallowed the main bulk of the meal but frequently at this stage the antrum is distended and early changes in the mucosa may be completely obliterated (Fig 1).

Malignant Disease of the Stomach

The stomach is one of the commonest sites of malignant disease. In 1953, in England and Wales, carcinoma of the stomach accounted for 18·5% of male and 15·5% of female deaths registered as being due to malignant disease (McKenzie 1956). In the fourteen years, 1946 to 1959, 470 cases of carcinoma of the stomach were seen at University College Hospital; 36% of these were classified as arising in the pylorus or pyloric antrum. The surgeon or pathologist with the stomach in his hand is occasionally wrong when trying to decide whether a lesion is malignant or benign, and it is assumed that the radiologist has an impossible task. It is therefore of great importance to know how frequently a carcinoma of the pylorus is misdiagnosed by the radiologist. The barium meal reports on 67 consecutive proven cases of carcinoma of the pylorus were inspected with the results shown in Table 1. Reports reading 'probably a carcinoma' were considered correct. These examinations were carried out by all members of the

Table 1
Carcinoma of pyloric region

Number of cases	67	
Radiological report correct	58	(86·6%)
Radiological report incorrect	9	(13·4%)
Incorrect Radiological Reports		
Pyloric stenosis due to benign ulceration	7	
No abnormality	2	1 patient with linitis plastica 1 patient with very large malignant ulcer and filling defect

department from the most junior to the most senior consultant. On review of the misdiagnosed group, a filling defect indicating the presence of a malignant growth was visible in 4 and a correct diagnosis could therefore have been made in 92·6% of the whole series. Such retrospective diagnosis is of course very easy but it is clear that careful X-ray examination of the intact stomach can lead to a correct diagnosis in a high percentage of cases. In the absence of pyloric obstruction there was little difficulty in recognizing the true nature of a malignant ulcer. Concern over the differential diagnosis of uncomplicated benign and and malignant ulceration did not occur.

Fear of being unable to distinguish between benign and malignant ulceration is one factor which is responsible for the radical surgical approach advocating early excision of all pyloric ulcers with its consequent operative mortality and post-operative morbidity. Another factor responsible for the radical surgical approach is the fear of malignant degeneration of a gastric ulcer.

In this series of 67 cases of pyloric carcinoma, one patient gave a history of hæmatemesis from a gastric ulcer thirteen years before being seen at University College Hospital. In another a peptic ulcer perforated (site unspecified) sixteen years before and 2 patients had a previous history of duodenal ulceration treated by gastro-enterostomy. This series is too small to draw any definite conclusion but Smith & Jordan (1948) reported 330 gastric ulcers treated medically and only 2 patients developed a carcinoma. The risk of malignant change is a controversial subject but it appears that it may not exceed the mortality rate of gastrectomy and when this is balanced against the five-year cure rate for malignant disease of the stomach there seems to be little justification for immediate surgical treatment of the apparently benign peptic ulcer.

Carcinoma accounts for the vast majority of cases of malignant disease of the stomach; gastric sarcoma is rare. Malignant change may occur in benign tumours; we have encountered one such case in which a leiomyoma became malignant. Secondary involvement of the stomach from adjacent lymph glands is not uncommon in the lymphomata but the stomach is rarely the site of the primary tumour. In 5 cases a lymphoma appeared to arise primarily in the lymphoid tissue of the stomach with involvement of only the drainage glands and in 1 patient there was a multifocal origin from the stomach and rectum. These 6 patients have been seen in a series of 400 lymphomata and compare with 517 cases of gastric carcinoma in the same period (Table 2).

Table 2
Primary gastric lymphoma

Number of cases	6	Hodgkin's 2 Lymphosarcoma 4
Site involved: Whole stomach 2, fundus 1, pyloric region 3		
Total number of lymphoma during same period	400	
Number of gastric carcinoma during same period	517	

Radiologically the lymphomata may present as filling defects, gross thickening of the mucosal folds, multiple tumours or as a diffuse involvement producing a linitis plastica. The appearances are indistinguishable from a carcinoma but extensive involvement of the duodenum may suggest the correct diagnosis. The following 2 cases illustrate primary lymphoma of the pylorus.

Case 1 Male, aged 74. Six months' history of vomiting, four months' poor appetite and upper abdominal pain. On clinical examination there was no abnormality. Barium meal demonstrated a large dilated stomach with food residue and an elongated narrow irregular pyloric canal with a filling defect (Fig 2). A partial gastrectomy was performed; histology showed a lymphosarcoma of the pylorus.

Case 2 Male, aged 40, with two years' history of attacks of vomiting increasing in frequency and severity. A gastroenterostomy had been performed a year ago at another hospital. Barium meal (Fig 3) showed a gastroenterostomy; the pyloric region was occupied by a large mass with superficial ulceration and thickened mucosal folds. The duodenal mucosa was also abnormal. At gastrectomy a large mass was found involving the pylorus and duodenum, nodular submucosal masses extended up to the gastroenterostomy stoma. On histological examination a diagnosis of Hodgkin's disease of the stomach was made.

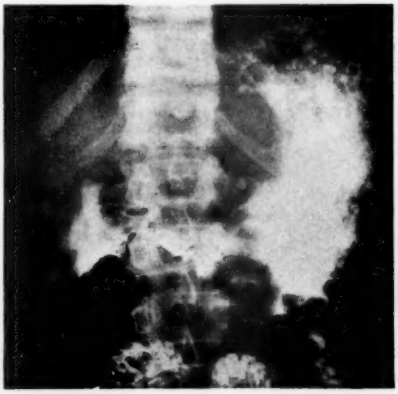


Fig 3 *Hodgkin's disease of the stomach*

Benign Tumours

Benign tumours of the stomach are surprisingly common but the great majority are very small, do not produce symptoms or signs and exist unrecognized. A post-mortem series from the Mayo Clinic (Rienits 1930) showed the presence of benign gastric neoplasms in 16% of 200 consecutive post-mortem examinations. James (1956) gives their incidence as 2% of all gastric tumours. At University College Hospital over the past ten years benign tumours have accounted for 2·8% of all gastric tumours. They are classified in Table 3. The only common benign tumours are adenomata, myomata and the neurogenic tumours; these are most commonly seen in the pyloric region of the stomach. Despite their comparative rarity they are of considerable importance because they may present clinically with dyspepsia, hæmorrhage or pyloric obstruction. Malignant change occurs particularly in the adenomatous polyp, the leiomyoma and the neurogenic tumour. This change is said to occur in 10% of neurogenic tumours and Stewart (1929) reported that of 263 cases of carcinoma 13 were associated with adenomatous polypi. In our small series sarcomatous change has occurred in one leiomyoma. The radiological features of these tumours are too well recognized to need repetition but the following cases illustrate some of their main features:

Table 3
Benign tumours of the stomach (modified from James 1956)

1 *Epithelium*	(*a*) From gastric mucosa: Adenoma single or multiple
	(*b*) From ectopic epithelium: Aberrant pancreatic rests
2 *Connective tissue*	Fibroma
3 *Neurogenic*	Neurilemmoma, neurofibroma
4 *Adipose tissue*	Lipoma
5 *Vascular tissue*	Hæmangioma, lymphangioma
6 *Smooth muscle*	Leiomyoma
7 *Cysts*	Dermoid, enterogenous, hydatid

Case 3 A woman, aged 40, presented with three months' history of recurrent attacks of abdominal pain associated with severe vomiting and upper abdominal distension. Barium meal demonstrated a very mobile pedunculated adenomatous polyp in the antrum. Her symptoms were presumably produced by intermittent pyloric obstruction either from blockage of the pyloric ring by the tumour or by induction of a gastric intussusception.

Case 4 A man, aged 44, presented with two years' history of abdominal pain and recent loss of weight. A barium meal (Fig 4) showed a small spherical tumour protruding into the base of the duodenal cap. At operation a round submucous tumour was found and histological examination showed this to be an adenoma arising in a pancreatic rest.

Case 5 A woman, aged 26, presented with a history of two years' abdominal pain occurring five to ten minutes after meals and relieved by alkalis. Barium meal demonstrated a round filling defect in the pyloric antrum. Gastroscopy showed no abnormality. At laparotomy a submucosal adenomyoma was found.

Case 6 A man, aged 45, presented with two weeks' history of severe epigastric pain and melæna. He subsequently developed a subphrenic abscess. Barium meal demonstrated a large mass occupying the whole of the pyloric antrum and the base of the duodenal cap showed the signs of hypertrophy of the pyloric muscle. At operation a large dumb-bell tumour was found, a spherical mass $1\frac{1}{4}$ in. in diameter was firmly embedded between the left lobe of the liver and the falciform ligament and this communicated by means of a thick pedicle $\frac{1}{2}$–$\frac{3}{4}$ in. in circumference with a large spherical intragastric mass 2 in. in diameter. Histologically it was shown to be a fibro-leiomyoma.

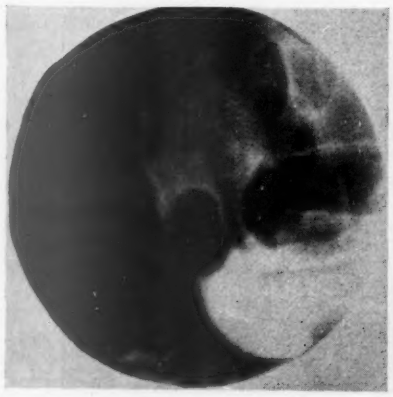


Fig 4 *Pancreatic adenoma in the base of the duodenal cap*

Fig 5 *Adult hypertrophic pyloric stenosis*

Adult Hypertrophic Pyloric Stenosis

Hypertrophic pyloric stenosis is a rare cause of pyloric obstruction in the adult. Cicatricial stenosis of a peptic ulcer and carcinoma are much commoner and in the last few years at University College Hospital only two cases of adult hypertrophic pyloric stenosis have been diagnosed preoperatively.

Hypertrophic pyloric stenosis in adults is divisible into two types: an *idiopathic* form in which there is no other demonstrable lesion in the gastro-intestinal tract and a *secondary* form which is associated with some other lesion such as peptic ulceration of the stomach or duodenum or tumour of the stomach. Its ætiology remains in doubt; it has been said to be the result of long-continued spasm and its association with other lesions in the adjacent stomach and duodenum supports this theory. It has also been attributed to a degeneration of the myenteric plexus of the pylorus and to congenital causes due to persistence of the infantile form of the disease.

This I think is the more likely explanation. It has been established that the congenital form may persist into adult life and in a recent series of cases (Nielson & Roelsgaard 1956) 78% of adult patients who had been treated medically during infancy for congenital pyloric obstruction were found to have persistent narrowing and elongation of the pyloric ring. Furthermore the male preponderance seen in the infantile form of the disease is also present in the adult. Pathologically the circular muscle of the pylorus is increased in thickness from the normal 3–8 mm to a maximum of 30 mm with an average of 15 mm.

In the adult the diagnosis is rarely considered. Patients present with vomiting and abdominal pain. Frequently the symptoms have been present since childhood but they may also first appear in adult life, most commonly in the fifth decade and signs of obstruction may quickly develop. The radiological signs are elongation and narrowing of the pyloric canal, the thickened muscular ring producing a mushroom-shaped impression on the base of the duodenal cap. The mucosa within the pyloric ring retains a fine linear pattern. Identical X-ray appearances can, of course, be produced by submucosal infiltration of the pylorus by a malignant growth.

Case 7 A man, aged 51, presented with a three-year history of upper abdominal pain, worse after meals, and for two months he had complained of vomiting and loss of weight. On examination there were no abnormal physical signs. Barium meal (Fig 5) demonstrated elongation and narrowing of the pyloric ring and a distinct impression with a convex upper border on the base of the duodenal cap. At laparotomy a firm lump the size of a grape was palpable in the stomach wall at the pylorus. Histological examination showed hypertrophy of the pyloric muscle and chronic inflammation of the mucosa.

Case 8 A man, aged 32, presented with a twelve-year history of pain across the chest occurring half an hour after meals. The attacks lasted about two weeks and were separated by intervals of freedom of two to three months. On examination there was tenderness in the epigastrium but no other abnormality. Barium meal showed increased resting juice with thick mucosal folds. The pylorus was elongated but showed little narrowing and a normal mucosa. No peristaltic waves were seen to pass through the narrow segment. At operation there was marked hypertrophy of the pyloric muscle extending proximally over a distance of 1 in. from the pyloric ring.

Fig 6 *Secondary hypertrophic stenosis associated with gastric carcinoma*

The secondary hypertrophic stenosis of the adult may be associated with tumours or ulceration of the stomach and duodenum. Fig 6 illustrates hypertrophic pyloric stenosis associated with a carcinoma of the pyloric antrum. Histological examination showed no evidence of malignant infiltration of the pylorus.

REFERENCES

James T G I (1956) *Ann. R. Coll. Surg. Engl.* **18**, 228
McKenzie A (1956) *Brit. med. J.* ii, 204
Nielson O S & Roelsgaard M (1956) *Acta radiol., Stockh.* **45**, 273
Rienets J M (1930) *Proc. Mayo Clin.* **5**, 364
Shanks S C (1950) *Proc. R. Soc. Med.* **43**, 117
Smith F H & Jordan S M (1948) *Gastroenterology* **11**, 575
Stewart M J (1929) *Brit. med. J.* ii, 567

The Pylorus: Its Function and Some Surgical Considerations

by H Daintree Johnson FRCS (*London*)

I shall first describe the mechanism of gastric emptying, as I see it, based upon the work of Quigley (1942) and others, and upon my own observations and consistent, I believe, with the findings reported by Dr D A W Edwards (p 930).

It is an observable fact that peristaltic waves in the stomach do not always meet across the lumen. Yet when they do not meet no delay in gastric emptying results. A peristaltic wave which fails to obliterate the lumen makes the same sort of contribution to gastric emptying as is made to the emptying of a bath by swishing the water towards the waste-pipe with the hand.

The stomach undergoes occasional bursts of 'hunger spasms' which I consider have nothing to do with gastric emptying; indeed, they mostly occur when the stomach is empty. Manometric studies (Fig 1) have shown that, except during the hunger spasms, intragastric pressure remains fairly constant, and is unaffected by peristaltic activity. There is simply a constant steady squeeze due to muscle tone.

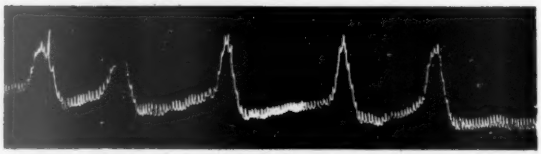


Fig 1 *Kymograph tracing showing changes in intragastric pressure in a man aged 51 with twenty years' history of duodenal ulcer: (1) Respiratory effect (frequent small wave at 20 per min), (2) tonus waves (just discernible undulations at 3 per min, probably peristaltic), and (3) intermittent spasms of the whole stomach (tallest peaks – occurring at 1–2 min intervals). (Reproduced from Orr & Johnson 1947, by kind permission)*

The duodenal cap behaves quite differently from the stomach and resembles a little muscular bag undergoing rhythmic systole and diastole. During diastole intraluminal pressure is slightly below that in the stomach, but during systole it rises above the gastric level. This observation proves beyond doubt that during duodenal cap systole its cavity is separated from that of the stomach.

Through a gastroscope the pylorus can be observed to be open most of the time. As a wave of peristalsis passes down the antrum and reaches the pylorus, the latter is seen to close. It remains closed for only a few seconds and then relaxes again, remaining open until it is reached by the next peristaltic wave.

The function of the pylorus may be deduced from these observations. Its purpose, I suggest, is not to prevent material from flowing from stomach to duodenum, which indeed ordinarily occurs throughout cap diastole under the influence of gastric tone. *Its purpose is to prevent reflux into the stomach during cap systole.*

The tone of the second part of the duodenum is high, as is shown by the difficulty in filling and demonstrating this segment radiologically. Indeed, I have found its internal pressure to be higher than that of the stomach. If it were not for the pylorus, contraction of the duodenal cap would partly empty the cap back into the stomach instead of wholly into the second part of the duodenum.

The whole mechanism of gastric emptying closely resembles, on a less vigorous scale, the mechanism of the heart; the auricle taking the place of the stomach, the ventricle that of the duodenal cap, and the mitral valve representing the pylorus. The difference between the high pressure in the aorta and the low pressure in the great veins and auricle is paralleled by the high tone of the duodenal second part and the lower pressure in the stomach. Like the heart, the gastroduodenal pump drives fluid from a region of low pressure to one of high pressure.

Since the pressure in the second part of the duodenum is higher than that in the stomach the pylorus is quite unnecessary for preventing material from leaving the stomach too quickly. The fact that it has no such function is well demonstrated by the old experiment of exteriorizing the duodenal cap of a dog. The stomach contents all escape at once and the pylorus shows no capacity to retain them.

The pylorus is not essential for the working of the gastroduodenal pump, though the pump is less efficient without it and much more reflux of bile into the stomach occurs. This is seen after gastrectomy with gastroduodenal anastomosis, when stomach emptying proceeds fairly normally. However, the free entry of bile into the stomach often causes nausea and bilious vomiting, one of the most troublesome of postgastrectomy complications. After Polya gastrectomy with gastro-

jejunal anastomosis, the zone of high pressure in the second part of the duodenum has been bypassed and gastric emptying is abnormally influenced by gravity. In the erect position emptying is often precipitate, and a patient who has had a gastrectomy sometimes has to lie down after meals to relieve the symptoms of 'dumping'.

Scarring from a duodenal ulcer interferes with cap systole and slows down gastric emptying by preventing normal diastolic filling. At operations for so-called pyloric stenosis narrowing of the canal is often not in evidence at all. Indeed, scarring of the pyloric canal itself may cause pyloric incompetence instead of stenosis. The stomach then dilates for the same reason as the auricle dilates in mitral incompetence with regurgitation.

By pyloric stenosis the clinician now means the clinical picture accompanying gastric retention, and it would be wrong to assume that he can differentiate between gastric retention due to antral stenosis, duodenal stenosis, true pyloric stenosis or pyloric incompetence. The term pyloric stenosis covers them all. Stenosis of the canal itself is a relative rarity.

'Functional' Obstruction and 'Organic' Obstruction

Clinically it is customary to distinguish between so-called functional and organic obstruction. The essential difference between them is that functional stenosis is reversible. It is due to the œdema and spasm associated with ulcer activity and will respond to antacid therapy. Pure organic obstruction is due to scarring and more often than not the ulcer is healed. To treat pure organic pyloric obstruction by diet and alkalis is a waste of time. There is no alternative to surgery.

However, the largest clinical group of patients have neither pure organic nor pure functional obstruction, but a combination of scarring and the œdema and spasm of an active ulcer. These patients respond best to a period of medical treatment followed by surgery after a few weeks. Obstruction and gastric retention due to œdema and spasm alone – without scarring – is uncommon, but is seen occasionally and these patients do not necessarily have a bad prognosis without surgery.

Effects on Gastric Secretion

Pyloric obstruction has an interesting effect on gastric secretion. So-called free hydrochloric acid usually disappears from the resting juice and may not be found even after histamine injection. This used to be said to be due to destruction of the power to secrete acid due to gastritis brought on by retention. It was recognized that stomach washing would cause a return of the acid, and this was held to be due to cure of the gastritis. However, a single thorough stomach wash may achieve this result, which would be a remarkably quick cure of gastritis if this were really the explanation.

A more likely explanation is that, in the presence of retention, secreted acid is mopped up, neutralized, and buffered by the retained food residues, mucus and swallowed saliva, so that its presence is masked. As soon as all this material has been adequately washed out the plentiful presence of hydrochloric acid may again be demonstrated. Indeed the patient is usually found to secrete acid excessively (Fig 2, Table 1).

The mopping up of acid by material retained in the stomach exerts an important curative effect on a duodenal ulcer, and pyloric stenosis, when it becomes marked, usually results in the healing of an ulcer beyond the obstruction.

However, retention of protein in the stomach has another effect. It is apt to promote prolonged secretion of gastrin and hence of hydrochloric acid. This acid retained in the stomach may not menace the duodenum, but often succeeds in undermining the defences of the stomach itself.

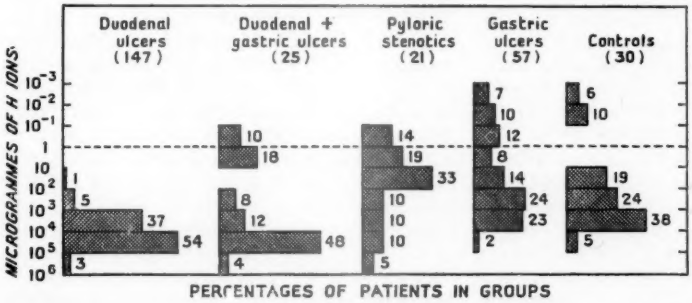


Fig 2 *Micrograms of ionized hydrogen in whole of gastric night secretion. The figures for the concomitant-ulcer group are seen to lie between those for duodenal ulcer and for pyloric stenosis. (Reproduced from Johnson 1955, by kind permission)*

Table I
Acid secreted at night (Johnson 1955)

	Percentages in groups				
Milli-equivalents free HCl in bulked all-night juice	*176 Duodenal ulcer*	*25 Duodenal and gastric ulcer*	*30 Pyloric stenosis*	*80 Gastric ulcer*	*30 Controls*
Achlorhydric	0	24	30	42	40
0–9	30	16	23	40	47
10–19	27	24	20	5	7
20–29	14	20	10	6	
30–39	9	4	3	4	
40–49	9	8	3	2	3
50–59	3			1	
60–69	1				3
70–79	3		3		
80–89	2	4	7		
90–99	1				
100–109	1				
110–	1				

Hence gastric ulceration is a not uncommon complication of gastric retention (Johnson 1955) and the combination of a gastric ulcer with gastric retention may be difficult to demonstrate radiologically. The usual sequence of events when duodenal and gastric ulcer are present together is that the duodenal ulcer appears first. The patient then develops some gastric retention and a gastric ulcer appears.

A gastric ulcer may complicate gastric retention from any cause unassociated with achlorhydria. After observing that gross retention often followed vagotomy when, years ago, it was performed without a simultaneous drainage procedure, I speculated that gastric ulcer would be a sequel (Johnson 1948). In due course gastric ulcers began to appear, and this is one reason why the operation of vagotomy alone had to be abandoned. I have also twice seen benign gastric ulcers in stomachs obstructed by small prepyloric carcinomas.

The important thing for the surgeon to realize is that patients with combined duodenal and gastric ulcers are hyper-secretors of acid, like duodenal ulcer subjects, and not hypo-secretors like other gastric ulcer patients. He must therefore treat them radically, and not with the very conservative Billroth I procedure now rightly becoming increasingly popular for most gastric ulcers.

The clinician's main concern in pyloric obstruction should always be to make sure he does not mistake a malignant lesion for one due to a peptic ulcer. Some years ago I was asked to see a woman of 24 who had been treated for four years for a duodenal ulcer. In the final month of a pregnancy she began to vomit with increasing frequency and severity, and radiography showed her to have pyloric obstruction. Labour was induced prematurely. Immediately after parturition I operated on her and found a large unresectable carcinoma.

Organic pyloric stenosis, whatever the cause, is a dangerous condition carrying substantial mortality. A cancer cannot always be excluded radiologically, but this is only one of the reasons why organic pyloric stenosis should always be treated surgically as soon as recognized.

REFERENCES

Johnson H D
(1948) *Postgrad med. J.* **24**, 193
(1955) *Lancet* i, 266
Orr I M & Johnson H D (1947) *Lancet* ii, 84
Quigley J P (1942) *Arch. Surg., Chicago* **44**, 414

Section of Physical Medicine

President R W Windle MD

Meeting April 12 1961

President's Address

The Action of Ultraviolet Light on Bacteria in Industry and Medicine

by R W Windle MD (*Hove*)

It was in 1877 that a remarkable paper was published in the *Proceedings of the Royal Society*, by Downes and Blunt, concerning researches on the effect of light upon bacteria and other organisms. The investigation was made to see if light exerted any appreciable influence, favourable or the reverse, upon the development of bacteria, or other organisms. They compared the effect of sunlight on bacterial solutions in test tubes, some of which were exposed or insolated, while others were encased by covering with thin sheet lead.

'In the large majority of cases, the exposed tubes remained clear for an indefinite time and in every instance were conserved for a distinct period, after their encased companions had become turbid. The most marked differences in the conduct of the two sets of tubes were obtained, when the sun shone brightly: when, for a period of a day or two, at the commencement of the experiment, the weather was close and sultry and the sky dull, the conservative effect of light appeared to be less pronounced.'

With these simple experiments, the two authors established that solar radiation has an effect on bacteria, but, even more remarkable was the fact that they stumbled on the effect of penicillin though, at that time, eighty-four years ago, the significance of their discovery was not understood. They stated that in the course of their investigations they found that when bacteria appeared early, and in large numbers, the mycelium of penicillium was rarely seen, the bacteria apparently preoccupying the ground; when, however, the development of the bacteria was, from some cause, retarded, or prevented, tufts of delicate mycelium submerged in the experimental solutions were frequently found.

The reduction of ill-health, the speeding of recovery and the saving of lives, would have been enormous during these years, and especially during the 1914–1918 war, if only the significance of this finding had been perfectly understood, but the effect of penicillin on bacteria remained unknown until Fleming made his great contribution to medical science.

On more than one occasion, the use of general ultraviolet light (UVL), has been attacked as being useless and one contributor to a medical journal, a year or two ago, took the hæmoglobin levels of a group of children before, and after, a course of UVL. The result did not show any improvement of the hæmoglobin levels, and the author stated that UVL was therefore useless, but such investigations are not worthy of our scientific training. Some years ago, an outbreak of hæmolytic streptococcal infection occurred among the nurses in a fever hospital. Attempts to eradicate this organism from the carriers by means of oral, nasal and parenteral penicillin met with no success, and it was only after I had irradiated their nasopharyngeal cavities with UVL that negative swabs were at last obtained. I refused requests to publish this information as I considered that there was insufficient proof, and there were no adequate controls, but the possibility of UVL being useful in selected cases remained for further investigation.

Radiations from the sun probably derive their energy from nuclear reactions. They emerge from the sun's outer layers and, after 8 minutes' journey, reach the earth's surface, where some of the UVL is absorbed by the atmosphere. Measured in Ångström units (Å) the ultraviolet spectrum can be seen to start at 4,000 Å where it overlaps the visible rays. For practical purposes ultraviolet rays can be further subdivided into 3 groups: (1) 4,000 down to 3,150 Å. These rays pass through most kinds of glass and have practically no erythemic action. (2) 3,150 to 2,800 Å, which are erythemic and pigmenting rays. This group also activates ergosterol to form vitamin D. (3) Below 2,800 Å the rays have a strong germicidal effect, but they may also give rise to a mild erythema.

Germicidal Effect of UVL

If bacteria are irradiated with different wave-

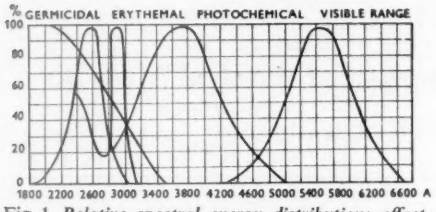


Fig 1 *Relative spectral energy distribution: effect in spectral wavebands.* (*Reproduced by permission of Philips Electrical Ltd*)

lengths and with an identical exposure for each wavelength, a graph can be drawn to show the optimum lethal dose (Fig 1). The peaks of the erythemal and germicidal curves occur at 2,800 and 2,600 Å respectively, the curves thereafter falling very rapidly. The low-pressure mercury arc delivers 60% of its electrical energy into radiation of wavelength 2,537 Å and this wavelength produces 85% of the maximum germicidal effect on most bacteria, viruses and fungi (Fig 2). For this reason the low-pressure mercury arc is most suitable for industry, where the bactericidal effect is the main consideration, as it is 5 to 10 times more efficient in germicidal action than high-pressure arcs, and is particularly suitable for the protection and disinfection of many products, which are so unstable that conventional methods of sterilization cannot be used. Some hospitals also make use of it to limit cross infection in children's wards. In the bakery trade, the presence of mould spores causes great trouble, and UVL can be employed to reduce airborne contamination.

Cheese is another food product which requires attention to prevent spoilage from surface moulds, as these may gain access during the maturing period and in the storage rooms. It has been found that a low intensity of UVL with a wavelength of 2,537 Å will effectively check the growth of moulds.

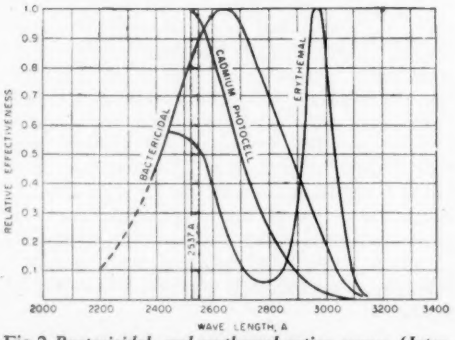


Fig 2 *Bactericidal- and erythemal-action curves.* (*International Commission on Illumination, Berlin, 1935; reproduced from Hollaender, 1935, by kind permission*)

Other uses in medical laboratories have been the sterilization of cabinets when growing viruses and the prevention of contamination during the filling of ampoules by machinery. Further investigation has shown that organisms differ in their response to UVL. For instance, *Esch. coli* is more susceptible than *Shigella sonnei*, but the exposure necessary to kill any one kind of organism varies considerably, temperature, illumination and environment all having a deciding factor. For instance, *Esch. coli* in a humid atmosphere requires four times the exposure of *Esch. coli* when airborne. Visible light has a contra effect to UVL and the lethal effect of UVL is reduced by luminous rays. This power of luminous rays of a wavelength greater than 3,600 Å has a protective action, which is known as reactivation, and heat also has a similar value in assisting recovery in bacteria, which have been irradiated with UVL. The germicidal effect of UVL is governed by exposure, that is to say intensity multiplied by time, and the basic factors in exposure are the incident power, the time and irradiated area. The intensity varies with the distance, mostly as the square of distance from the irradiating source. Experiments with UVL radiation on the mature spermatozoa of drosophila (quoted by Swanson & Stadler 1955) showed that both mutations and chromosomal aberrations were induced by exposure to UVL, and that the frequency of mutations was higher when mating of the irradiated males followed immediately after treatment. No mutations were transmitted five days after the irradiation and it was proved that the radiation was capable of causing early death of the irradiated flies. It was considered, therefore, that a further study of UVL on other forms of life might have practical applications. Lwoff & Gutmann (1950) discovered that UV irradiation produced, in some lysogenic strains of bacteria, a massive lysis, accompanied by liberation of mature phage, and it appeared that the UVL had in some way removed the linkage. It was therefore of interest further to investigate the action of UVL on bacteria and the following experiments were devised and carried out:

(1) To demonstrate, by artificial means, the findings of Downes & Blunt (1877) a blood agar culture plate was sown with *Staph. aureus* and after the plate had been half-screened, it was irradiated for 30 minutes. The result showed a kill in the exposed half, with a small growth in the shadow. A control plate was also irradiated before sowing, to ensure that the UVL had not altered the culture media by the formation of ozone, but there was no difference in the result. Further tests were now made by preparing a blood agar plate and dividing it into six sections. An overnight broth culture of *Staph. aureus* was prepared and

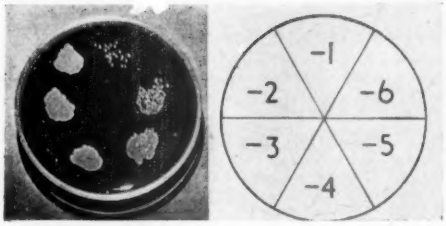


Fig 3 *Culture plate sown with* Staph. aureus *in dilutions from* 10^{-1} *to* 10^{-6}

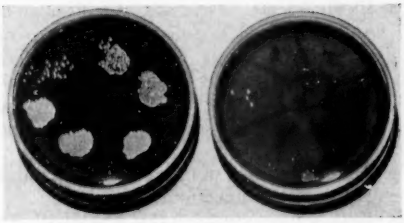


Fig 4 *The effect of irradiation with Kromayer for 60 seconds at 5 in. distance on cultured plate (right) compared with unirradiated control (left)*

diluted from 10^{-1} to 10^{-6}. The original culture solution was estimated to contain approximately 50 million organisms per millilitre and one drop of each dilution was now placed in each section so that overnight incubation clearly showed the extent of growth (Fig 3). The effect of UV irradiation on a similar plate can be clearly seen in Fig 4, the plate on the left being the control and the plate on the right having been irradiated at 5 in. for 60 seconds.

(2) The same organism, a coagulase-positive staphylococcus from the nose, was used to test different exposures at different distances. Exposures varied from 1 to 30 seconds. There was no evidence of a kill at a distance of 5 in. in any of the series. At $1\frac{1}{2}$ in. distance, both at 1 second and 3 seconds exposure, there was no kill, but 80% kill was achieved with 10 seconds, and at 30 seconds exposure there were only 2 survivors out of an initial 200,000 organisms. Comparative studies were made in order to contrast the total amount of radiation, using the same organism and varying the distance and time factor. In the last experiment it was found that an 80% kill was achieved by irradiating at $1\frac{1}{2}$ in. for 10 seconds, but in this series, a 99·9% kill was produced by a 15-second exposure at $1\frac{1}{2}$ in. and this was found to approximate roughly in killing effect to a 60-second exposure at 5 in.

(3) To compare the lethal effect of the standard Kromayer and the low-pressure mercury arc duplicate plates were prepared and inoculated with drops of overnight broth culture of *Staph. aureus;* the result (Fig 5) shows quite clearly the more lethal effect of the Kromayer lamp. The lethal effect of the Kromayer at 20 seconds is comparable to the low-pressure mercury arc at 90 seconds. The output of the latter is almost exclusively at 2,537 Å, but has only an output of 0·4 watts, whereas the Kromayer lamp has a heterogeneous line spectrum, ranging from 1,850 to 4,000 Å with a total output of 60 watts. The output of the Kromayer at 2,537 Å is estimated to be about 1·5 watts, which, being at least four times more powerful, would account for the difference in lethal action between the two series.

(4) The next experiment was designed to test the comparative sensitivity of various organisms, and the organisms selected were salmonella, pathogenic *Esch. coli*, proteus, *Shigella sonnei*, with a pool of all the organisms and a control. Broth cultures were prepared as before, with dilutions of 10^{-1} and 10^{-3} and these were irradi-

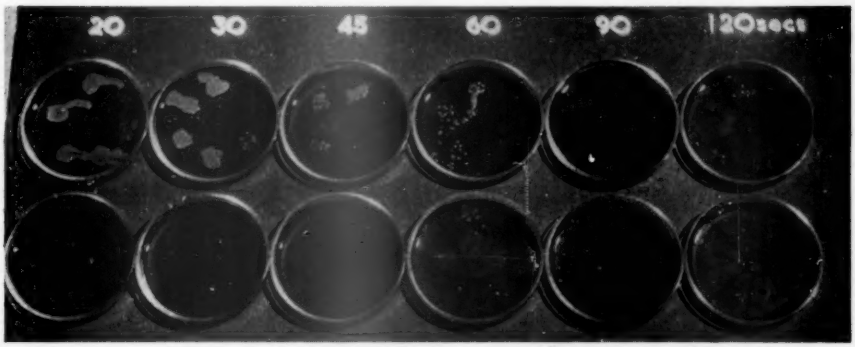


Fig 5 *The lethal effect of UV is compared between two sets of equally cultured plates when irradiated at different times from 30 to 120 seconds. The top row was irradiated with the low pressure mercury arc, and the bottom row with Kromayer*

ated at 10, 30, 45, 60, 90 seconds, at a distance of 5 in. Out of 200,000 organisms, the surviving organisms were as follows: Salmonella 6; pathogenic *Esch. coli* 15; proteus 2; *Shigella sonnei* 100; pool 33 survivors. Of the pool 23 were shigella, 3 *Esch. coli* and 2 proteus; there were no salmonella.

The confluent growth in the control containing all the organisms was uncountable.

It is worth while comparing this result with the lethal effect on *Staph. aureus*, which clearly shows that some bacteria are more resistant to the effect of UVL than others. It was now decided to see what effect repeated dosage of UVL had on bacteria. Two series of mixed cultures of *Shigella sonnei* and *Esch. coli* were prepared and exposures of 30 seconds and 60 seconds given at the following times: 0 and 1 hour; 0, 1 and 2 hours; 0, 1, 2 and 3 hours; 0, 1, 2, 3 and 4 hours; 3 hours after plating; 4 hours after plating; 3 and 4 hours after plating.

The results are shown in Table 1. First, the *Shigella sonnei* are everywhere more sensitive to UV radiation than the *Esch. coli*. Secondly, the increased number of radiations has made no appreciable difference in the survival rate, when irradiated at the time of plating and again one hour later. It is also apparent that if given the chance to multiply for three hours, the survival rate increases, but is reduced by a further application of UVL, one hour later. It is clear that bacteria are most sensitive to radiation in the logarithmic phase, but it must be emphasized that results obtained *in vitro* are not necessarily the same as those from *in vivo*, as the lag phase *in vitro*, when bacteria are growing in size ready to multiply in great numbers, may be vastly shorter, or even absent *in vivo*. This observation can only be determined by clinical trials, and even then must be conducted with sufficient numbers, to obtain a true assessment of value.

Table 1

Survival rate of *Esch. coli* and *Shigella sonnei* following repeated irradiation with UVL 2,537 Å

		Esch. coli	*Shigella sonnei*
0 and 1 hour	60 sec	2	0
	30 sec	100	0
0, 1, 2 hours	60 sec	0	0
	30 sec	0	0
0, 1, 2, 3 hours	60 sec	0	0
	30 sec	1	0
0, 1, 2, 3, 4 hours	60 sec	2	0
	30 sec	1	0
3 hours only	60 sec	100	1
	30 sec	100	1
4 hours only	60 sec	200	1
	30 sec	300	1
3 and 4 hours	60 sec	16	0
	30 sec	17	0

(5) The next experiment was designed to find out whether there was any synergistic action between UVL and the antibiotics. Four organisms were chosen: (1) The Oxford staphylococcus, penicillin sensitive. (2) *Staphylococcus aureus*, penicillin resistant. (3) *Salmonella*. (4) *Esch. coli*. Each plate had four strips of the selected bacteria

Fig 6 *The effect of irradiation together with antibiotics is seen on four different strains of organisms. Irradiated with Kromayer at 30, 60 and 90 seconds. The antibiotics were penicillin (grey strip) and streptomycin (white strip). In Series A the antibiotics were placed on the culture media 2 hours before irradiation; at the same time as irradiation in Series B, and 2 and 4 hours after irradiation in Series C and D respectively*

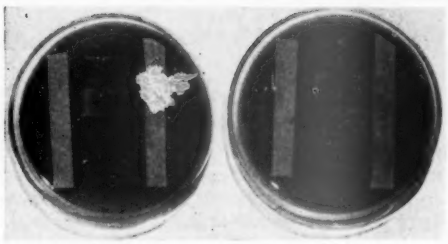


Fig 7 *60 seconds irradiation with Kromayer 2 hours before application of antibiotics (right) is contrasted with unirradiated control (left)*

sown horizontally, and the antibiotic was applied by means of two strips of blotting paper, one being soaked in a solution of penicillin of a strength 50 units/ml and the other in streptomycin. Four series were made of four plates each and were all irradiated at 30, 60 and 90 seconds respectively. Series A was irradiated and then incubated for two hours before the application of the antibiotic strips. B, The antibiotic strips and irradiation were applied simultaneously. C, The antibiotic strips were added at the time of plating, but irradiation did not take place until two hours later. D, As for C, but irradiation was four hours later. The effect of the antibiotics which had received no irradiation is clearly seen in Fig 6, the controls being on the left-hand side, where the lower two control plates have been removed for the sake of clarity. In series C and D, where the organisms were not irradiated until two and four hours respectively, after the antibiotic strips had been added, there appears to be very little difference from the controls. It would seem that irradiation at the time when no active growth of the bacteria is occurring is therefore of no value.

In series A, where irradiation with UVL took place two hours before the antibiotics were added, there is a marked change, particularly after 60 seconds irradiation. The bacterial growth of the penicillin-resistant strain of staphylococci can be seen to be diminished. Fig 7 shows the 60-second slide of Series A, alongside its control for comparison, to emphasize the reduction of bacterial growth of all four organisms. A slight increase of destructive effect is apparent when antibiotic and irradiation are applied at the same time, so that this may have some useful application in clinical work. It is obvious however, that irradiation with UVL must be given before, or at the time of, application of antibiotics so that bacteria are in an active stage of growth.

We have come a long way from the days of Heliopolis, when the sun was worshipped as a god, but we have come to understand many of the physical properties of the sun's electro-magnetic waves. The bactericidal action of UVL is being unfolded, but is it not possible that we still have something to learn and that there is an even greater therapeutic action in the sun's rays than we realize at the present time?

Acknowledgment: I am indebted to Dr J E Jameson for help with the preparation of the bacteriological experiments.

REFERENCES
Downes A & Blunt T P (1877) *Proc. roy. Soc.* **26**, 488
Lwoff A & Gutmann A (1950) *Ann. Inst. Pasteur* **78**, 711
Swanson C P & Stadler L J (1955) In: Radiation Biology. Ed A. Hollaender. New York; **2**, 249

Meeting March 8 1961
at the North Middlesex Hospital
Edmonton

Mr T M Hennebry delivered a short paper on **Cartilage Restoration Following McMurray Osteotomy.** He showed X-rays of several patients in whom the joint space had increased following this operation and discussed its possible explanation.

The following cases were shown:
(1) **Delayed Partial Recovery More than Ten Years after a Facial Nerve Graft**
(2) **Polyarteritis Nodosa, Presenting with an Acutely Painful Calf**
(3) **Longstanding Rheumatoid Arthritis Complicated by Probable Systemic Lupus Erythematosus**
Dr J H Jacobs
Paget's Disease of Bone Treated by Radiotherapy
Dr V B Levison
Polyarthritis with Behçet's Syndrome
Dr I R Ferdinand
Diffuse Systemic Sclerosis Treated with Relaxin
Dr J Arnold
Polymyositis with Unusual Clinical and Electromyographic Features
Dr E D R Campbell

Meeting June 10 1961
at the Royal Air Force Medical Rehabilitation Unit, Headley Court, nr Epson. Surrey

The following papers were read:

Health and Fitness of Aircrew
Air Vice-Marshal Sir Aubrey Rumball
Some Problems of High-speed and High-altitude Flight
Air Commodore W K Stewart
Plastic Surgery and Physical Medicine
Air Commodore G H Morley
The Role of a Rehabilitation Unit in the Treatment of Head Injuries
Group Captain P J O'Connor

Meeting May 10 1961

Richard Kovács Lecture

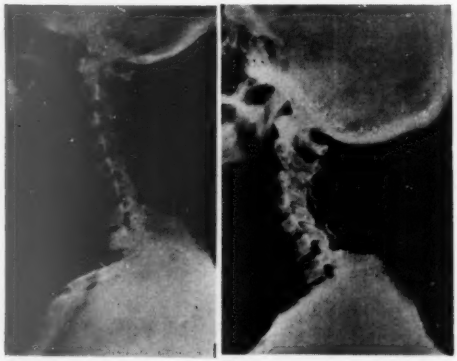
Kovács and After [*Abridged*]

by P Bauwens MRCP (*London*)

With the untimely demise of Richard Kovács in 1950, the world of physical medicine lost its Boswell. I speak with some feeling in this matter, for I had the privilege of meeting him in New York in 1939 and of reviewing his last book ten years later. This book was not only a record of what constituted physical medicine at the time of publication, but also showed the trend and the direction this was being given, and I shall not hesitate to use it loosely as my text.

It is surprising that in so comprehensive a book published in the U.S.A., where osteopaths and chiropractors flourish, there should be no mention of manipulative and mobilizing techniques of proven value in the treatment of painful derangements of intervertebral structures. For it seems that something effective can occur in selected cases as the result of well-executed if somewhat esoteric manœuvres. This is illustrated by Fig 1, which shows two lateral views of the cervical spine of a patient suffering with a long-standing painful stiff neck. Before treatment the spine was abnormally straight with a marked tendency to kyphosis – probably due to spasm of the flexors of the neck. After two manipulations the spine assumed a more normal lordosis.

While in medicine there exists a not unreasonable inclination to administer substances in an isolated and purified form rather than in combination with others as they occur in nature, such an improvement on nature has proved most unfortunate in the case of artificial light therapy.



A B

Fig 1 *Lateral X-ray views of the cervical spine of a patient with a painful stiff neck:* A, *before, and* B, *after, manipulation*

Man, no less than green plants, has successfully evolved in such rays from the sun as reach the earth. The spectral composition and the energy distribution of these rays are well known. That they are not harmful and are probably indispensable to life is accepted, but whether they have a positive therapeutic value is still considered debatable. The reason for this, as I see it, is an unhappy concatenation of circumstances which started with the advent of the quartz mercury vapour burner as a source of radiation.

Kovács in his book mentions that 'There is a considerable difference between this type of radiation and that of the sun' and he further goes on to explain its popularity as follows: 'The simplicity of handling and up-keep has made the hot quartz lamp the most widely used source of artificial light.' He was sufficiently enlightened not to say '*of artificial sunlight*' for the quartz mercury vapour lamp never was and – in its present form – never will be a substitute for sunlight.

The reason for this difference is now moderately clear, but it was not so over a decade ago. In the first place, it is now appreciated that the two erythema-producing wave bands of the ultraviolet spectrum do not operate in the same manner. Nor have they the same penetrating power. The curves in Fig 2 show the erythemal effectiveness of ultraviolet rays (UVR). One wave band in the region between 3,100 and 2,900 Å, has a peak at about 2,960 Å and another band begins in the shorter wave range of the spectrum at about 2,800 Å nearing a peak around 2,500 Å. The sun spectrum contains only the first of these while the quartz mercury vapour lamp emits a considerable proportion of its energy in the latter.

In all probability the erythema produced by the quartz lamp results from the absorption of these short rays which are totally foreign to sunlight.

Green plants, which, like man, thrive on sunlight, are affected by these two biologically effective wave bands. Fig 3 throws some light on this. The experiments were carried out on tomato plants and the broken line shows the lethal effectiveness of the various wave lengths in the UVR spectrum on them. The most striking feature is that the curve produced wellnigh follows the contours of that of the erythema-producing radiation which is absent from sunlight.

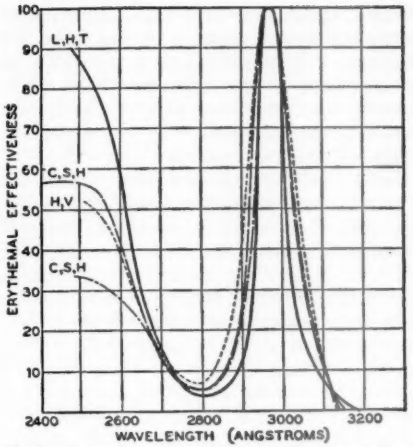


Fig 2 *Curves showing the erythema-producing effectiveness of various waves in the UV portion of the spectrum*

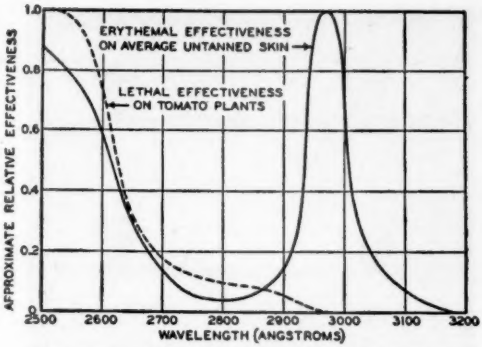


Fig 3 *Spectral lethal effectiveness of ultraviolet energy for leaves of tomato plants compared with spectral erythemal effectiveness for average untanned human skin*

Figs 2, 3 and 4 are reproduced from M Luckiesh, 'Applications of Germicidal Erythmal and Infrared Energy'. Copyright 1946, D Van Nostrand Co., Inc., Princeton, New Jersey

In the light of the foregoing observations, it is interesting to examine the results and conclusions of an experiment carried out on human beings, for the well-conceived report presented was misinterpreted by the profession at large. I refer to the Medical Research Council's report on 'Artificial Sunlight Treatment in Industry' (Colebrook 1946).

The object of this experiment was not to prove or disprove the therapeutic value of UVR but simply 'to ascertain in a scientifically controlled experiment whether the collective irradiation of workers by UVL from quartz mercury arc lamps will reduce their rate of sickness absence and the duration of their colds'. Extravagant claims had been made to the effect that a reduction in absenteeism resulted from exposure to the rays from such sources, in doses of the order of the 'minimal perceptible erythema' dose. The experiments were carried out on statistically significant numbers of volunteers at the Admiralty, at Vauxhall Motors, and at South Kirby Colliery.

The technique, which was advocated by the devotees of the quartz lamp, was meticulously adhered to for the group treated with the full range of UVR from the lamps. A control group was treated in a similar manner save that glass screens, which cut out all radiations below 3,300 Å, were interposed between the burner and the subjects. A second control group remained completely untreated.

The group subjected to the unfiltered radiation absorbed sufficient radiation with a lethal effect on tomato plants to produce a minimal perceptible erythema. It is doubtful whether, with the dosages thus stipulated, the subjects absorbed anything approaching an effective quantity of those erythema-producing rays present in the sunlight spectrum. Those treated with the screened lamps clearly received no radiation with any claims to biological properties.

Because of the terms of reference of the Committee set up to answer the very restricted question, the experiment as it was carried out totally excluded from its accounts the biologically most active wave band in sunlight. That is the one between 2,900 and 3,100 Å. The records showed that 'the persons treated with the shorter UVR did not differ significantly from those irradiated but not receiving these rays' in any of the respects indicated.

As a matter of fact, with Fig 3 still in mind, it would have been equally justifiable to conclude that the treatment of man with small doses of the brand of UVR which is particularly lethal to tomato plants does not benefit him. On seeing Fig 4, which illustrates this effect, it is tempting to render thanks to Providence that the results did not demonstrate that radiations from mercury vapour lamps were actually deleterious.

I find it quite impossible to resist the temptation to interpolate a hypothetical analogy in order to stress my point. It is, of course, common ground that fresh air makes for rosy cheeks. There is, therefore, no reason why an enterprising person should not at some time have started marketing compressed air in cylinders. Suitably advertised as originating from the Alps or pine woods, it might have been said to possess beneficial properties, particularly in smog-bound districts. But suppose now that another person – far cleverer than the enterprising one – argued that pink

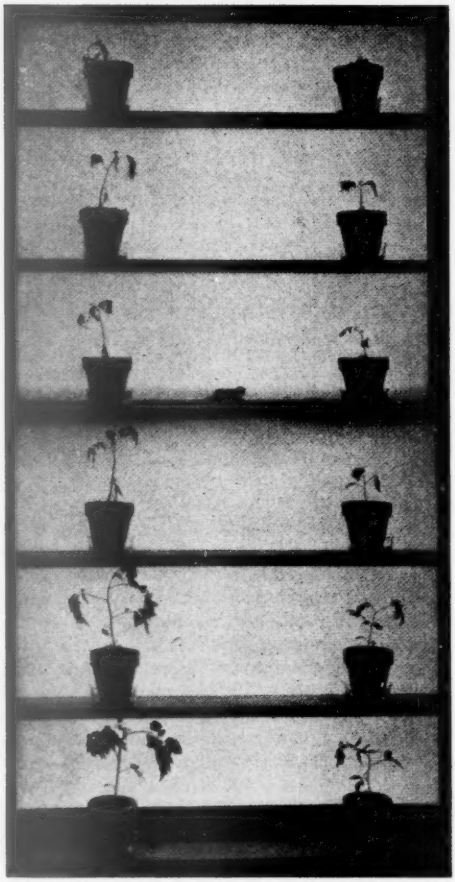


Fig 4 *Effect of irradiation of tomato plants with varying doses of UVR of wave lengths shorter than 2,800 Å. Those on the top shelf received 1·9 microwatts per sq. cm and died after twenty-four hours. Those on the bottom shelf, 0·14 microwatt per sq. cm showed slight damage after 500 hours*

cheeks could be achieved much more rapidly by replacing part of the oxygen by carbon monoxide, and on these grounds entered into competition with Pure Pinewood Air Ltd.

A time might come when the extravagant claims for this adulterated product became the object of an enquiry and the deductions drawn from a set of statistically valid experiments might well be that no substantial difference was found in the general health of those subjects who twice a week were made to breathe small quantities of this product, and of those who were made to breathe this gaseous mixture, after the removal of both pink-making gases – that is oxygen and carbon monoxide. This, of course, would only apply when small doses were involved – say minimal perceptible cherry-lip doses – for we know the consequences of inhaling carbon monoxide in large quantities. This, however, would be a reasonable conclusion and furnish the correct answer to a specific question as to the value of the 'Pinker than Pink' product.

It is hard to say whether such deductions would be generally misconstrued to imply that air or oxygen are of no value. The chances are that they would be if the same mental processes were brought to bear on the subject as was done in respect of the M.R.C. report. Some will fail to see the import of my excursion into fiction. Others with vested interests will no doubt strive to find arguments against it.

It would be too much to expect a reversal not of the M.R.C.'s verdict, which was unexceptionable, but of the misconstruction put upon it. What can, however, be done is to urge those who make use of artificial light therapy to employ sources which approximate natural sunlight, and to resist the temptation in this case to improve on nature. This is no problem now that it is possible by means of fluorescent phosphors to produce practically any spectrum – within reason.

Photobiology has made great strides in recent years and attention has been drawn to unsuspected phenomena of photosensitization, photoreactivation and to the synergic and antagonistic effects of certain waves on living organisms. These mechanisms may one day explain why the full solar spectrum is of greater value than its component parts and why adulteration should be avoided.

Of course, there are other aspects of physical medicine which have evolved since the publication of Kovács' book ten years ago. Some because of the application of new principles, others through expansion of already recognized ones. Muscular exercise, which at one time was thought of in crude terms of the number of times a weight was lifted, has now become a science in which cybernetics of control of movement play their part. Neurophysiologists have demonstrated that locomotion is produced by means of a servomechanism; that repetitive stimulation is necessary for the maintenance of synaptic function; that repetitive stimulation produces potentiation and that disuse can produce a sort of synaptic lethargy. There is, therefore, a great deal of theoretical and practical evidence that in cases of dysfunction of a system every method of promoting activity should be exploited. The dictum that function creates the organ seems to be receiving scientific support, and may well become a maxim. The day may even come when it is similarly established that demands on a biological system not only promote its development and its

efficiency, but also accelerate repair processes. As far as the nervous system goes it certainly appears as if activity – albeit momentarily in abeyance – might accelerate certain repair processes. Here, at least, there exists histological proof that a normal motor neuron will adopt denervated muscle fibres through distal branching and formation of new neuromuscular synapses. Whether this process is accelerated by stimuli impinging on the anterior horn cells which have to produce the additional axoplasm required for this extension is not known. As far as I am concerned, it is still an act of faith, as of course it must be with others.

Taking the treatment of anterior poliomyelitis as an example it is interesting to see how universal, in an entirely empirical way, the principles of production of excitation of the anterior horn cells have been. From Sister Kenny with her 'think here', accompanied by prodding of tendons to the neuromuscular facilitation, to the more recently introduced procedures of pinching muscle or brushing the skin and of eliciting some postural reflexes, all these tend to the same end – the ultimate excitation of anterior horn cells at the appropriate level.

Personally, I am more direct. I stimulate nerves with volleys of electrical impulses not so much with the object of producing muscle contraction by stimulation of degenerated motor neurons as of stimulating the afferent component of nerves in the hope that the impulses will ultimately impinge on those anterior horn cells unable to discharge their function. One might liken this to the exploitation of a frustrated Hoffmann-reflex.

While on the subject of muscular exercise it may be pertinent to mention the place of electrically produced exercise in the physiotherapeutic armamentarium. Modern teaching holds little brief for faradic stimulation in the treatment of muscle atrophy on the grounds that where the nerve supply is intact this method achieves nothing that cannot be accomplished by resisted exercise. It is more than probable that this view stems from an erstwhile exaggerated use and prescription of faradism in and out of season coupled with an over-readiness to condemn electrotherapeutic measures. My feeling is that faradism has a very definite place in therapy and that the indications for its application are well defined.

The question which arises is: What does faradic stimulation produce which does not occur in normal exercise? First of all, on maximal stimulation, all muscle fibres are synchronously stimulated. This provides for a greater tension than is possible by voluntary contraction controlled and mediated by a feed-back mechanism. Secondly, the faradic current also stimulates the afferent component of the nerve supply to treated muscle.

Although in a normal or only moderately wasted muscle, voluntary exercise causes adequate afferent impulses from the various intramuscular sensory organs, this may not be the case where muscle wasting is gross or where resisted muscle contractions cause pain. Considering that the afferent impulses bring about an excitatory state of the anterior horn cells supplying the contracted muscle and an inhibitory state of those of the antagonists, it is reasonable to infer that faradic stimulation is indicated in gross wasting and where resisted exercise causes pain. Its use is unjustifiable in the absence of these indications. At the same time, the form of voluntary exercise should always be appropriate to the condition. For instance, to attempt to build the quadriceps by heavily resisted exercise in degenerative conditions of the knee-joint appears to me as the infliction of an unnecessary trauma and an excellent way of increasing the wear and tear of joint surfaces. Such exercises should be static in so far as they should cause no relative movement of the joint surfaces. If possible they should be executed with the least damaged joint surfaces in apposition and outside the painful range. The situation is entirely different in non-degenerative and non-inflammatory conditions of the joints where resisted exercise through full ranges of movement may be indulged without fear of complications.

A form of electrical treatment not mentioned by Kovács, possibly because it could not be rationalized, is the use of a painful stimulus in the treatment of localized pain or tenderness for which there seems to be no cause and which may be the result of an obscure vicious circle, sometimes explained by saying that pain engenders pain. However, a possible explanation based on physiological principles can be proffered for the existence of such conditions and their response to this homœpathic form of treatment.

It is common ground that every form of excitable tissue has a threshold below which stimulation is ineffective. What is perhaps less well appreciated is that these thresholds can fluctuate. If they decrease, an otherwise ineffective stimulus excites the structure. Local tenderness can be explained in terms of low thresholds and of painful stimuli being fired off at the slightest provocation. Spontaneous pain on the other hand is produced when the threshold falls below the zero line, that is to say below the point at which no stimulation at all is required in order to evoke a response. The situation is one at which autoexcitation occurs. If in certain conditions thresholds can drop so as to cause local tenderness and pain, they can also be raised.

One way of achieving this is by exploiting the capacity for accommodation which most excitable structures possess to various degrees.

Accommodation is brought about by a rise of threshold in the presence of progressively increasing but ineffective stimuli. In terms of pain or discomfort it is a form of capacity for adaptation to background stimulation – a kind of acclimatization. The technique, which in my department is dubbed 'the Chinese torture', is applied as follows:

In a case of coccydynia, a small electrode is connected to a generator of any form of painful current, and is applied over the tender or painful area. The circuit is completed through a large indifferent electrode. The current is then progressively increased and kept for a few seconds at an intensity which is only just tolerable to the patient and is then more rapidly reduced to zero. This is repeated several times. If it is successful in an amenable condition, the pain may be considerably reduced. The emphasis here is on the production of the maximum sensory stimulation with the minimum of muscle contraction. To this end, an old Spamer faradic coil is more suitable than the Bristow coil, but better still is a generator of alternating current of between 4,000 and 6,000 cycles per second. It is clear that this would constitute a futile form of treatment where the pain is due to disc lesions and then would merely be an exercise in pointless sadism.

In an attempt to find a final topic more closely related to Kovács' book, I rashly decided to open the book at random and comment on whatever subject presented itself. Not being a gambler, and knowing approximately where the chapter on 'Newer Methods of Electrodiagnosis' was situated, I cheated a little. Alas, the fateful pages 148–149 were twenty pages away from those hoped for, and they dealt with medical galvanism in general and the electrogalvanic bath in particular. The electrogalvanic bath depicted on page 149 by courtesy of Teca Corporation (Fig 5) looked the epitome of efficiency and highly sanitary. I thought it might in the first instance be interesting to compare it with its counterpart of a half century earlier (Fig 6). The question is: What had been claimed for this elaborate equipment and its intricate operational technique?

Kovács states that 'The electro-chemical effects of the galvanic current employed in the bath bring about chiefly a stimulation of the skin and of the nervous system'. In the same paragraph he adds that 'Clinically there appears to be a definite influence in the general well-being and appetite of patients'.

These two non-committal comments are worthy of a little thought. It is a fact that those interested in medical electrology have studied with care the action of the galvanic current at the level of the electrodes. Much is known about the iontophoretic, electrophoretic, electrotonic and electroosmotic effects immediately under the electrodes. It was soon realized that these polar effects were superficial and could have no influence on deeper structures, except as regards stimulation of excitable tissues at make and break of the current.

The fact that ions foreign to the body and with pharmacological actions could be introduced into it by iontophoresis was demonstrated in various ways. Leduc's experiment whereby he poisoned two rabbits by means of potassium cyanide iontophoresis under the cathode and strychnine sulphate iontophoresis under the anode is a classic. So is Chatzky's (Fig 7) which demonstrated how iodine ions migrated towards the anode in a potato, and there produced the typical purple stain of the starch iodine complex. Another experiment (Fig 8) by the same worker showed how the slightest cross-flow of a sodium chloride solution readily prevented the iodine from reaching the anode.

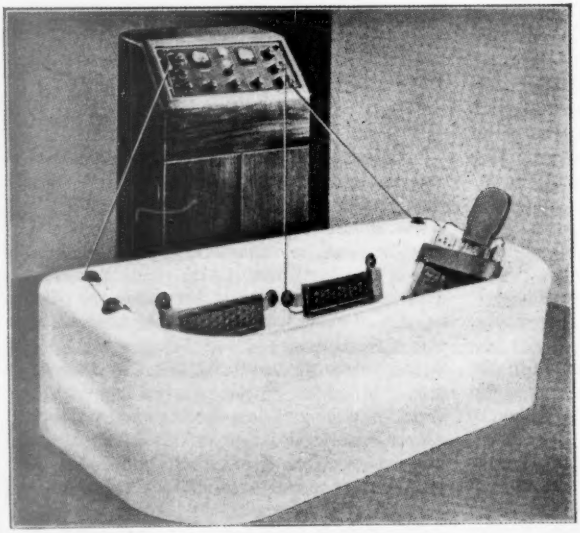


Fig 5 *The electrogalvanic bath of the Teca Corporation illustrating Kovács' 'Electrotherapy and Light Therapy'*

All these experiments were conceived to demonstrate the efficacy of direct current in introducing therapeutic ions into the body and causing their migration in it. However, it could be deduced from Chatzky's second experiment that few ions introduced through the skin would get beyond the

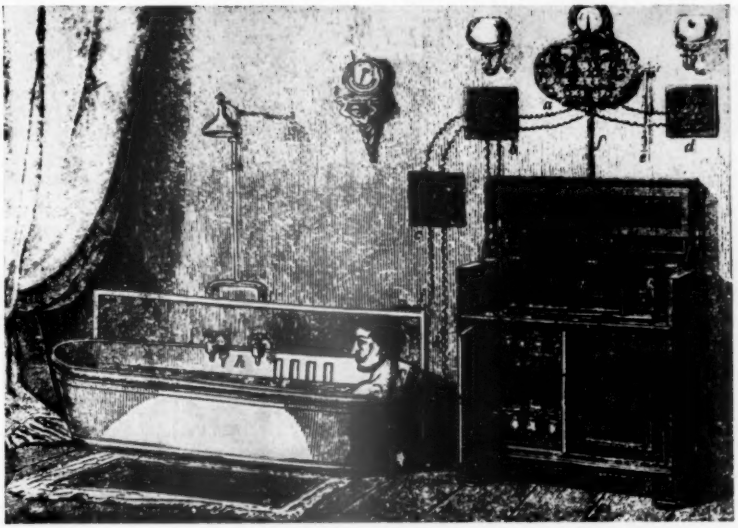


Fig 6 *The electrogalvanic bath's ancestor of a half century earlier. This is not a Victorian form of suicide, but a gentleman of that era indulging in a little 'constant and faradaic current application'. (Illustration from the G.E.C. catalogue of 1886)*

capillary network in the dermis. Nevertheless, let us enquire whether those experiments to which I have alluded have not some application throughout the path of the current.

The tissues between the electrodes consist mainly of living cells, intercellular fluids and blood vessels. They are inter-related in so far as the cells depend for their well-being and their behaviour on their environment which is the intercellular fluid, the composition of which is controlled by the exchanges between the blood and the stationary fluids across the capillary walls.

From Leduc and Chatzky's experiments it would seem reasonable to expect that under the influence of an electric field this exchange as far as ions and charged colloids were concerned would be accelerated.

It is possible to demonstrate that this acceleration does take place by means of the following experiment: A solution of potassium iodide, of which the iodine is radioactive, is poured into a collodion sock which is itself immersed in a sodium chloride solution.

A Geiger counter, of which the collimator has been adjusted to monitor the radioactivity of the collodion sock content, shows that this changes very little during the experiment implying that there is but little escape of the radioactive iodine ion into the surrounding electrolyte.

On turning on the direct current the following changes may be observed: Within a few minutes the radioactivity of the content of the sock will drop considerably, and a state of equilibrium will be reached between the ambient fluid and that in

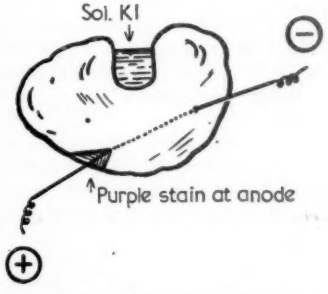


Fig 7 *Chatzky's experiment demonstrating that the iodine ions from a solution of potassium iodide contained in a well gouged out in a potato reached the anode and there produced the purple, starch-iodine complex*

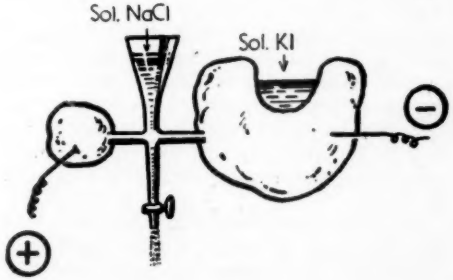


Fig 8 *Chatzky's second experiment with two potatoes demonstrating how even a slow cross-current of sodium chloride solution prevented the iodine ions from reaching the anode without interrupting the electric current*

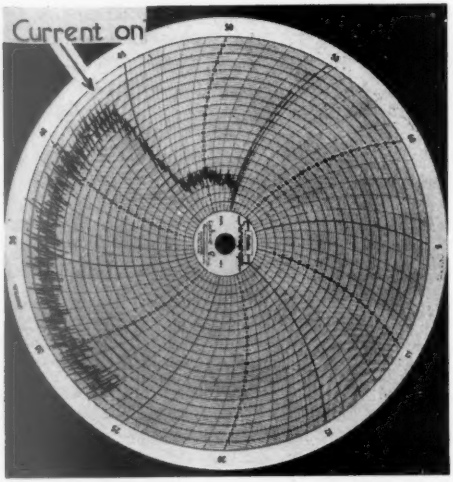


Fig 9 *Polar record of the radioactivity of the potassium iodide in a collodion sock showing the rapid drop in local radioactivity after the constant current has been turned on.* (*Time in minutes*)

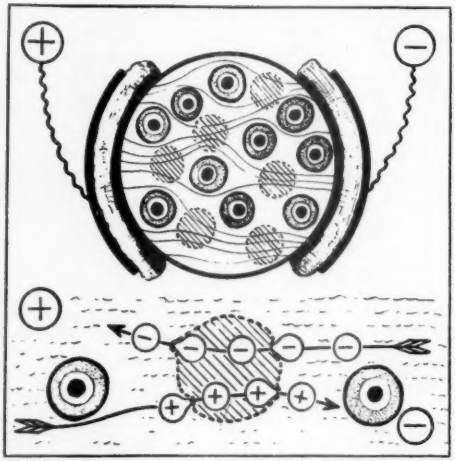


Fig 10 *Diagrammatic representation of the probable interpolar action of direct current on living tissues. Above, lines showing direction of iodine migration passing through the permeable capillaries but not through the cells because of the relatively high resistance of the peripheral protoplasm. Below, accelerated interchange between ions of the intercellular and circulating fluids across the vessel walls under the influence of the electric field*

the sock, showing that the interchange of ions has been substantially accelerated by the potential gradient between the electrodes (Fig 9).

Translated into terms of tissues and their components (Fig 10), it must be obvious that throughout the electric field there must occur an accelerated interchange of ions between the stationary intercellular and the circulating fluids.

To the question, could this have any effect, I am inclined to answer, 'Yes'. But this would merely be an exaggeration of what goes on normally. It might certainly produce that feeling of well-being and increase of appetite mentioned by Kovács in the case of electrogalvanic baths.

Another observation of the same order was made by Leduc who stated that the passage of the constant current through the head produced a sensation of mental freedom which facilitated thinking. At least one colleague in this country supports these findings and claims from personal experience that this treatment has sedative and restorative properties which barbiturates do not possess. Unfortunately, the technique is more complicated than the administration of a hypnotic by mouth.

It would be over-sanguine to expect more than this with simple galvanism, whether generalized or localized, but suppose that an ionized substance with some specific therapeutic effect – whether radioactive, antibiotic or anti-inflammatory – were ingested before or injected intravenously during the treatment, one might then be able to obtain a localization of the effect between the electrodes by virtue of the accelerated ionic interchange there.

The potentialities of this strike me as considerable and impel me to suggest some experimental work not only in this particular field, but in any field where a combination of pharmacological and physical agents appears to hold out promises.

My choice of topics may have appeared inappropriate for such an important occasion as the first Kovács Lecture. Yet every one of them is in some way related to Kovács' book, and it has been my endeavour to show that this book is by no means closed: indeed, that some interesting problems are still awaiting solution.

It is my hope that Mrs Kovács' generosity and the example of her late husband's industry will prove instrumental in furnishing answers to some of these and other conundrums in physical medicine triennially.

In conclusion, I should like to say how very honoured I feel to have been selected to deliver the first Richard Kovács Memorial Lecture and thus to have been given an opportunity of paying tribute to his work.

REFERENCES

Colebrook D (1946) Artificial Sunlight Treatment in Industry. M.R.C. Industrial Health Research Board, London; Report No. 89

Kovács R
(1949) Electrotherapy and Light Therapy. 6th ed. London

Luckiesh M (1946) Applications of Germicidal, Erythemal and Infra-red Energy. New York.

Section of Neurology

President W H McMenemey MD

Meeting March 2 1961

Pain in the Upper Limb

Mr J M Small (*Birmingham*)

The value of pain to mankind is undoubted. Without it the preservation and evolution of the species would have been impossible, but intrinsic pain, of no value to the organism, torments humanity. Endogenous pain, like endogenous depression, seems not uncommon to the clinician unable to find a specific structural lesion to account for it. Slowly, however, the patterns of pain associated with specific structural change have emerged, indeed, to such an extent that we risk becoming wedded to specificity. Yet there is no intrinsic pain pattern which may not have a number of causes, one or many at a time.

The intervertebral disc protrusion with root compression and anterior primary divisional pain is well known, and yet the interpretation of the posterior primary divisional pain remains, as it must, uncertain, awaiting more information or developments in individual cases.

The comparison of arm and leg pain is of some value, but the limbs are differently constructed and with entirely different functions. The upright posture of man has not been entirely to his benefit, and the evolutionary hopes in this respect have shown that uprightness is not free from painful consequences. In the leg the shearing strain of body weight in the lumbosacral area has led to disc disintegration and pain; ischæmic conditions of the legs have led to muscle pain on walking. Although these factors are fully at work in the arm they are not of the same importance in a limb that hangs from the shoulder girdle and has wonderful prehensile ability. In the arm peripheral neural and vascular compression plays a greater part in painful conditions.

In the finger is seen the combination of somatic and autonomic pain in tumours of the glomus – often invisible tumours, flamboyant in their pain manifestation. There may be shrinking from the touch which triggers intense pain, confined or spreading in the arm and sometimes associated with visible sympathetic over-activity. This pain is so like trigeminal neuralgia that such an origin in the face needs consideration but is denied by histology and natural history. But in this respect it is interesting that the sensory root of the V nerve contains efferent autonomic fibres in the same way as peripheral spinal nerves.

The first important contribution on the effect of compression on mixed nerves containing varying efferent and afferent fibres was made by Granit *et al.* (1944). In their experiment they divided the anterior and posterior nerve roots of the lumbar plexus and tied a ligature around the sciatic nerve. Stimulation of the anterior nerve root resulted in a 'short' of the neural impulse into the sensory fibres, the action current being recordable in the posterior root. They found that the ligature could be of such a compressing degree that the efferent impulse would pass it but still induce potentials in the sensory fibres. Removal of the ligature resulted in a return to normal in which no cross-circuiting occurred. Stimulation of the sensory root rarely led to activation of the motor fibres. In neural compression, therefore, a number of factors are at work, direct pressure upon sensory fibres causing pain, upon the motor fibres causing muscle spasm and 'induced' pain in sensory fibres. This probably also applies to autonomic efferent fibres.

The dependent upper limb leads to a variety of problems described in varying terms as 'thoracic outlet syndrome', 'costoclavicular syndrome' or 'scalenus anticus syndrome'. Quite apart from these names other varieties of compression by scalenus medius, the margin of Sibson's fascia, have all been held from time to time responsible for pain and symptoms in the upper limb. That they are all at times and to varying degree responsible for neurovascular compression there is no doubt. Pain is experienced by otherwise normal people wearing ill-fitting coats

or equipment causing a descent of the shoulder girdle. It is likely that congenital alterations of segmental origin of the brachial plexus are important, but so long as the seventh segment serves the middle finger the shoulder girdle is correct and satisfactory. Changes in this may lead to a cervical rib and neural pressure which may be complicated by aneurysmal dilatation of the subclavian artery with further nerve compression. The presence of two syndromes with cervical rib is well known: the ulnar syndrome, which is easily understood by compression of the lower roots of the brachial plexus, and the median syndrome, in which the ulnar portion may be less apparent. Varying explanations of this condition have been made, mostly based upon a cause directly related to the thoracic outlet and variations in innervation of the hand muscles. But it seems likely that the initial disturbance in the hand of ulnar type leads to weakness in the muscles maintaining the carpal arch, such as the palmaris brevis, and the opponens digiti minimi. As a result of this the palm flattens and there is compression of the median nerve in the carpal tunnel. The same condition may develop when the ulnar nerve is compressed at the elbow.

In publications on the 'carpal tunnel' syndrome great emphasis has been given to a specific change in this canal to account for the syndrome. It gives rise to painful, burning sensations chiefly in the median area of the hand and later causes thenar muscle wasting; it mainly affects middle-aged women, the pain occurring in the night and rendering the hand clumsy, partly insensitive and weak in the early morning. There is no doubt that such cases occur from local causes, e.g. acute dislocation of the semi-lunar bone; arthritic changes in the wrist-joint and tenosynovitis of the tendon sheath, acromegaly and pregnancy causing direct pressure upon the median nerve.

I believe the great majority of sufferers from the 'carpal tunnel' syndrome have no primary pathological change at the wrist. The primary lesion is descent of the shoulder girdle at the thoracic outlet or is in the spinal canal. It is often determined by the build of the patient, leading to a weakness of the ulnar musculature and flattening of the palmar arch, which is accentuated by use of the hand. There is median nerve irritation, and later weakness. It is from this that the patient seeks relief, and the cause is truly in the carpal tunnel – but not primarily so. In the cases in which I have divided the transverse carpal ligament I have not seen any local abnormality other than constriction. There can be no doubt that after prolonged compression secondary changes may occur in the synovial membrane and surrounding tissues, but it is no proof that these are the essential pathology.

Treatment

I have nothing to add to the standard treatment of cervical disc lesions causing root compression or of cervical ribs causing symptoms of compression.

In the last century stripping of the gluteal muscles was practised for the sciatic syndrome, and this must have relieved some of the posterior primary divisional pain syndromes, but division of the pyriformis muscle hopefully undertaken at the same time can have had no effect upon the anterior primary divisional pain due to disc protrusion. In the same way my experience of scalene section has suggested it is of little value. Obviously the abolition of neural compression, whatever it may be, is the important thing to do when other methods of treatment have failed.

Many people with the 'carpal tunnel' syndrome are relieved by splinting, and even more by rest and the wearing of a glove to maintain the carpal canal, or by having the hand bandaged in this position at night. Many, however, cannot continue with this regime and division of the transverse carpal ligament gives them relief. It is an excellent operation, giving immediate relief from pain and restoring function. It is usually a procedure designed to relieve compression of the nerve from outside.

The removal of a compressive factor may not always be enough, secondary perineural changes may maintain neural cross-circuiting and pain from motor activity. Freeing nerves is of great value.

Painful states are complex. We need to consider multiple factors rather than structural causes which can be seen in a museum.

REFERENCE

Granit R, Leksell L & Skogland C R (1944) *Brain* 67, 125

Dr J D Spillane (*Cardiff*) showed slides illustrating some anatomical and pathological features of the cervical spine in relation to sources of root pain.

Mr K I Nissen, Dr Ritchie Russell, Dr Marcia Wilkinson, Dr Roger Gilliatt, Dr John Walker, Dr Helen Dimsdale, Dr Barbara Carter and **Dr M N Pai** also took part in the discussion.

Meeting April 6 1961

Amnesic Syndromes

Sir Aubrey Lewis (*London*)

The Psychopathological Aspect

Many of those who made notable contributions to the psychopathology of amnesia have begun with an affirmation of the importance of memory function, using some such phrase as Janet (1898), who said at the opening of his report to the London Congress of Experimental Psychology: 'The part played by memory is of paramount importance in the functioning of the mind, and its smallest alterations have grave pathological consequences'. Such aggrandizement of memory is now out of fashion: psychologists concern themselves more with applying the theory of learning and of communication to its experimental study than with observation of its disorders, and clinicians are apt to look more closely at the limbic system than at dissection of the elements of retention and recall that seem to depend on the integrity of that system.

Consequently there has come about some confusion of terms. Whereas for clinicians the consummation of the memory process is the reappearance in consciousness of a former precept, for the psychologist the reappearance in consciousness is unimportant: what is significant is decay of inhibition, transfer, retroaction and other characteristics of change in performance over a period of time; these can be as well, or better, investigated on some motor task than on verbal reports of conscious recall. The psychologist is therefore ready to study memory in animal experiments; but the psychiatrist, and I think the neurologist, would have to re-examine his concept of remembering before he could comfortably follow suit. The psychiatrist finds it particularly difficult to dismiss consciousness from his concept of memory because he usually thinks of the active process of forgetting on Freudian lines, whether he is a psychoanalyst or not; and he is furthermore reluctant to extend the concept of memory because he knows how Semon and Bleuler and other clever men came to grief when they enlarged memory till it was almost coextensive with biology or psychology. Indeed the predominant state of mind of the psychiatrist in dealing with memory and its disorders is one of hopeful caution: he does not want to trip up over engrams, or premature localization, or screen memories, or any of the other traps for the unwary which he knows about, and he is disappointed at the relatively meagre advances made in the psychological study of this field during the last twenty or thirty years. But he is in no doubt of its importance – he would say, with Locke, that 'memory is an intellectual creature, is necessary in the next degree to perception. It is of so great moment, that where it is wanting, all the rest of our faculties are in great measure useless; and we, in our thoughts, reasonings, and knowledge, could not proceed beyond present objects, were it not for the assistance of our memories . . .'.

The Korsakoff Syndrome

In a consideration of amnesic syndromes the first question must be 'How many are there?' and the second 'What are their characteristics?' To this the psychiatrist has a short answer: 'There is one, and its typical features are those known by Korsakoff's name – severe defect of retention and other functions of memory, time disorder, disorientation and confabulation, without any corresponding impairment of consciousness or intellectual deterioration' (Korsakoff 1890). This, according to common usage, is the amnesic syndrome. There are, of course, disturbances of memory, sometimes startling and total, in other conditions, but the amnesia in them is not so central and conspicuous, and it does not so regularly concur with other psychological features as to constitute a clinical pattern deserving to be known as an amnesic syndrome. It may be urged that hysterical loss of memory has a strong claim to be so termed, but the manifestations of this condition are too varied and dependent on accidents of circumstance to make up a syndrome. Still, since syndromes are not handed down to us from on high and are merely provisional constructs it will do no harm if hysterical and other conditions in which memory fails are called amnesic syndromes. I shall, however, describe mainly what for the last sixty years has been the amnesic syndrome *par excellence*.

There are two familiar points which it is well to restate before any discussion of the Korsakoff syndrome: First that it may follow an extraordinarily wide variety of forms of cerebral damage or decay – general paralysis, Wernicke's encephalopathy, senile dementia, cerebral trauma, anoxia from strangulation, tumour, arteriosclerosis, encephalitis, poisoning by carbon monoxide, lead and other noxæ, artificially induced convulsions, epileptic states and many more diseases of the brain. Secondly, it centres on a function which has been dissected and redistributed

almost out of existence. As Bartlett (1932) put it 'It is perfectly true that nobody can put a ring around memory and explain it from within itself. The dissolving power of modern research seems to have split memory into a number of variously related functions. The functions may be many and yet, acting together, they issue in a specific process demanding its own name, and its own special modes of study'.

Nature of the Disturbance

The commonest division of memory is into the four stages – registration of impressions, retention, recall and recognition. The first of these, the learning phase, is that which was chiefly incriminated in the amnesic syndrome by the old masters – Wernicke, Bonhoeffer and Kraepelin. But though they regarded defect of registration as the chief, and perhaps the fundamental and essential, anomaly, they were aware of the indirect nature of their evidence: they inferred this defect because the patient had grossly inadequate immediate recall. Thus in Brodmann's investigation (1902, 1904) because the patients could not reproduce a sequence of eight or twelve nonsense syllables even after innumerable repetitions, he assumed that the repeated impressions had not been recorded fully. But he also satisfied himself, by Ebbinghaus's sparing method, that traces were left – traces which could only have been derived from impressions made during the learning process. Similar observations were made, in careful experiments by Gregor (1909), Schneider (1912), and Köppen & Kutzinski (1910), using words, series of pictures and incomplete sentences and figures. The choice of material to be remembered and the manner in which it is represented are of more importance than the earlier workers realized. André Rey (1959) has recently demonstrated that in dysmnesic patients concrete objects visually presented are recalled better than single words spoken aloud to the subjects: this difference is evident also in normal persons, but in the patients it may go so far that words are apparently not registered at all, while objects are.

A somewhat similar observation was lately made by Nyssen (1957): he found that Korsakovians (as he pleasantly calls them), even when very severely amnesic, can acquire, recall and recognize to some extent simple figures and words with concrete meaning if given sufficient opportunity to learn them through daily presentation and copying, but that figures are more easily recognized than words.

There is now abundant reason to conclude that although in the Korsakoff syndrome the immediate reproduction of recent impressions can be very defective, their subsequent recall or recognition may give clear proof that registration did occur, at any rate partially. The disorder must therefore be investigated also in other stages of the memory function or in other functions closely connected with memory, of which the most obvious is perception.

Pick (1915) and Grünthal (1924) were the first to conclude that thinking is the psychological area basically affected in this disorder and that the patient's prime difficulty lies in forming a mental set (*Einstellung*): his past perceptions are not available to him, he cannot relate them to a present situation. This finding was much elaborated by Bürger-Prinz & Kaila (1930) in the light of their experimental studies, and has been lately explored again in the thorough Boston inquiries (Talland 1958, Talland & Miller 1959) which showed the patients to have an inflexibility of perceptual set, a reduced capacity to shift attention, what might be called a dysdiadochokinesia of perceptual attitude. Tied, as it were, to the first object-stimulus he receives the Korsakoff patient cannot check and revise his subsequent percepts and interpret them successfully. This militates, of course, against their utilization in recall and may favour confabulation. Nevertheless, the perceptual disorder must be considered a minor and separate aspect of the amnesic syndrome: it is not sufficient explanation of the disorder of memory to postulate as its essence a disturbance of 'set', faulty perception and incapacity to grasp orientating events and relate them to one another.

Disturbance of Time

The second most striking anomaly in the Korsakoff syndrome is the disturbance of time. This invariable feature can be most readily recognized in the patient's temporal disorientation and in his jumbling of remembered events: he cannot order the succession in which they occurred. Though recognized by Korsakoff (1890) and Bonhoeffer (1904), this characteristic did not come into its own until thirty years ago. With the little burst of philosophical and psychological studies in time-experience that took place about that time, the Korsakoff disturbance was closely looked into, notably by van der Horst (1932, 1956) and by Ehrenwald (1931) and Krauss (1930). It was put forward as the basic disturbance. Van der Horst (1956) has maintained that the deficit is in respect of events that have once had personal meaning: whereas impersonal experience (for example, learning an algebraic formula or nonsense syllables) does not have a temporal sign attached to it and may not be demonstrably at fault when the customary psychological tests of registration and retention are applied, quite striking incapacity will be evinced in the same patient when he is questioned about the events of his personal life, *la vie vécue*. Personal events

cannot be recalled with normal sharpness and clarity unless they can be placed in time: but the Korsakoff patient, says van der Horst, has an impairment in his ability to place events plucked from the continuity of past experience, and all else that occurs in the Korsakoff syndrome is a secondary effect of his temporal incapacity. 'Time is the psychological category that enables us to distinguish between perceptions which are otherwise identical.' From this supposedly primary defect in temporal organization, van der Horst also ingeniously, but not quite plausibly, derived the retrograde amnesia, the reduplicative paramnesia, the confabulations and disorientation of Korsakoff patients.

The abnormality in temporal location, which van der Horst linked so closely to personal experience, has been formulated differently by other investigators such as Ehrenwald (1931), Krauss (1930), Lidz (1942) and, recently, Mouren & Felician (1958) in France, and Whitty & Lewin (1960) in this country. They rested their conclusions partly on experimental data. A good example of such a study is in the report by Williams & Zangwill (1950), who found that if a series of pictures had been exposed to moderately amnesic patients, the order was retained better when the consecutive exposures could be perceived as building a related sequence (e.g. the numbers 8, 9, 10) than when they consisted of disconnected items; they also noted a tendency to antedate recent events by pushing them further back into the past. They inclined to the view that disturbance of sequence-relation is a consequence of the retention-defect, and not the basic or primary disorder. Since the point at issue does not at present lend itself to decisive experimental inquiry, it is sufficient to recognize that the aspect of memory-function which deals with temporal order and relation is invariably disturbed in the amnesic syndrome, and that, as Bartlett (1932) pointed out, the capacity to pick out events from the series in which they occurred is probably a late acquisition, demanding 'special devices' for reconstructing schemata; these devices will be among the first to go when the neural substrate is damaged.

Confabulation

Confabulation is so picturesque a feature of the amnesic syndrome that it has received a good deal of attention, especially from the earlier writers. They explained it, rather too readily, as a defensive effort to hide failures of recollection: Bonhoeffer (1904) called it 'embarrassment-confabulation' (*Verlegenheits-konfabulation*), while admitting that the fantasies produced could take a wider scope than this interpretation would account for. We have to ask why these patients do not simply answer 'I don't remember', and why they accept their false memories as correct; also why some patients produce their confabulations spontaneously and in plenty, while others have to be prodded with suggestions and leading questions. There are clearly considerable differences between individuals in these perversions of memory, just as there are differences in normal activities of memory between one person and another.

There is in some confabulations a dream-like quality, suggesting that they may have had their origin in a preceding delirious state or in the hallucinations of nocturnal confusion, or even in actual dreams: in such patients the confabulations are less likely to be changed in response to suggestion. Long ago Wernicke pointed out that confabulations might originate thus out of a confusional state: they are not, then, strictly products of disturbed memory. Nor is confabulation a distinctively morbid activity. Bartlett (1932) showed in his classical monograph that normal remembering is not a mechanical affair of literal, exact reduplication: we do not summon and reproduce memories in the way that we repeat nonsense syllables, by rote; our memories are subjected to a constructive process in which condensation, elaboration, and invention play a leading part. Similarly in the Korsakoff state inventive fantasy plays a more important part in determining composite fabrications than does the need to compensate for defective recall. If we examine the content of the false memories we find, as Russell (1959) and Russell & Nathan (1946) pointed out, that fragments of past experiences have been dislocated from their proper temporal sequence and their context; they are mingled with perceptual data drawn from recent events or from the situation in which the patient is being examined at the moment.

Closer examination of the content of false memories suggests that much of what is remembered, and even more of what is forgotten, depends on emotional forces, such as psychoanalytic studies have elucidated (Flament 1957). Whereas Ebbinghaus, G E Müller and other pioneers in the study of memory ignored these affective influences, Bartlett stressed them in his vigorous revolt against the depersonalized analysis of memory, based on artificial situations. The catathymic influence of feeling-tone has been well demonstrated in systematic tests of patients with the amnesic syndrome. When, for example, they have to repeat the gist of short narrative passages that have been read to them, there is appreciably less distortion of affectively neutral passages than of disagreeable ones (Hartmann 1930, Talland & Ekdahl 1959). In Lindberg's (1946) thoroughly investigated patient, who had a very severe and typical Korsakoff syndrome attributable to prolonged alcoholism, his amnesia was most striking

and complete in matters referring to his fiancée, whose death had been a profoundly distressing event for him: in a word-association test, his reaction-time was most delayed when the stimulus word touched on the painful circumstances of their relationship. It follows from findings such as these that some at any rate of the forgotten memories may be difficult or impossible to recall, not because of damage to the neural substrate but because repressive or other emotionally determined forces hinder the appearance of the memories in consciousness. This is only to bring the amnesia of pathological states into line with normal remembering: cf. Darwin's reason for noting down adverse observations 'I had also, during many years, followed a golden rule, namely that whenever a published fact, a new observation or thought came across me, which was opposed to my general results, to make a memorandum of it without fail and at once; for I had found by experience that such facts and thoughts were far more apt to escape from the memory than favourable ones'. A catathymic explanation for some of the Korsakoff amnesia is consistent with the well-known fact that although such a patient cannot recall or recognize something once well within his knowledge, he may be able to reproduce it under hypnosis or in other facilitating circumstances: it may appear in his confabulations, or serve to shorten materially the time required to relearn it. An emotionally shattering experience can either distort (as in confabulation) or have the effect of repressing (as in amnesia) the recall of the event as a historical occurrence, and can operate outside consciousness to exaggerate or build upon those disturbances of memory which are the direct result of damage to cerebral structures. Striking instances of this have been reported in the Korsakoff syndrome after a suicidal attempt at strangulation: and it is, of course, a well-known aspect of retrograde amnesia after head injury.

Forgetting

But these catathymic influences are by no means the whole story. No one would now dispute that forgetting is an active process, not a mere passive fading with the lapse of time. There is, it is true, a curve of forgetting in which, as Ebbinghaus showed us, a rapid fall immediately after learning is succeeded by a general flattening out as the interval is extended. But the matter is more complex than this – and certainly more complex than our clinical methods of examination allow for. Although retention declines generally in proportion to the log of time, there can be considerable differences in the rate of decline, which will depend on the initial strength of the memory trace and of the factors which annul it. The latter are what chiefly concern us in pathological disturbances of memory. The strength of trace, however, will, both in normal and in Korsakoff subjects, itself depend on the success of the initial learning or perception, on the amount of repetition, i.e. relearning, on the kind of thing learnt or perceived, and the vividness of the initial experience to be remembered. It may also be reinforced by verbal formulation on the patient's part.

Among the factors which can annul the traces of a past experience and so prevent its recall, interference from a succeeding event has had the most attention from psychologists. This retroactive inhibition is most clearly in evidence when the two events are tasks in which the subject has to learn different responses to the same, or similar, stimuli: it is a laboratory phenomenon, which may or may not occur also when the casual events of daily life succeed one another. Whether it could be accountable for the amnesia of Korsakoff states was experimentally tested by Talland (1959) in the elaborate studies he has made in Professor Raymond Adams' department. The subjects were 14 women and 6 men with well-established alcoholic Korsakoff states: there was a control series of 23 alcoholic and neurological patients. The subjects were asked to learn words – 15 nonsense syllables and 20 real words – printed on cards and shown to them for three minutes each: they were then asked to recall as many of the words as they could. Then they were either given the same list to relearn or they were given a matched series of words and the procedure repeated for this list, after which they were tested with the first list again, to see whether the second learning task had interfered with the first. A similar procedure was followed in tests of recognition. The control group showed an increase in the number of syllables or words correctly recalled when they had had to relearn the same list, but this gain was reduced when a second, matched list had been interposed and the subject required to memorize it: in other words, in the control subjects there was clear evidence of retroactive inhibition. But the Korsakoff patients showed no gain in relearning, and no retroactive interference effects, whether tested by reproduction or recognition. It can be concluded that in Korsakoff patients who have a residual though poor, capacity for learning and retention, there is no evidence to suggest that their forgetting can be attributed to retroactive inhibition. Whether the converse phenomenon of reminiscence – improved recall after an interval of rest – occurs in Korsakoff patients has not, as far as I know, been investigated.

Another approach to the problem of forgetting has been by relating it to extinction (Woodworth & Schlosberg 1954). There are conspicuous differences between the two processes, of course,

but there are also similarities, notable in the way that an extinguished conditioned response can be spontaneously recovered after an interval. Without entering into a controversial field, it is worth recalling that in eyelid response conditioning to a buzzer, with a puff of air as the unconditioned stimulus, Korsakoff patients have shown abnormally rapid extinction; they also, as one would expect, were much less able to form conditional responses in the first place. This was demonstrated in the study made by Horsley Gantt & Muncie (1942) of a series of Korsakoff patients. The unconditioned stimulus was a painful faradic shock, the conditioned stimulus a light or sound. The experiments confirmed the importance of 'set', especially when reinforced by the patient's verbal formulation of what is happening, and they showed that a Korsakoff patient's ability to form conditioned responses is roughly proportionate to the severity of his clinical condition.

Distinctiveness of the Syndrome

In any survey of the problems of the amnesic syndrome, it is paradoxically evident that, remarkable and characteristic as are the clinical anomalies in this condition – the contrast, for instance, between the patients' retained verbal facility and his profound disturbance of memory – yet systematic examination of his memory reveals only quantitative differences between him and a healthy person of the same age. The extent of the quantitative differences can indeed be enormous, but still it is possible to detect in normal people the same essential phenomena occurring sporadically: we all have unexpected and unexplained lapses of memory, we all develop paramnesias, we all confabulate and have occasional disturbances in our time-attribution and sequence; even retrograde amnesia can be observed in healthy people after a severe emotional unheaval. The cognate similarity in quality, in spite of coarse and obtrusive differences in pattern and corrigibility, may be found between hysterical amnesia and some features of the organic amnesic syndrome. I do not mean to say anything so absurd as that a patient with hysterical amnesia exhibits the typical phenomena of a Korsakoff patient, but I suggest that there is nothing in the known psychopathology of hysterical amnesia which has not been observed in the organic cereoral syndrome. A dramatic instance was supplied by my patient (Lewis 1953) with partly arrested G.P.I. and a severe amnesic syndrome, periodically aggravated. He had developed, while in the United States, such apparently psychogenic dissociation that his amnesia was wholly attributed to this by an experienced observer, an authority on the psychological effects of brain damage, who wrote a book about this patient's symptoms and psychopathology; they were there interpreted as wholly hysterical (Franz 1933).

If we concede these points of close similarity between the psychopathology of the organic amnesic syndrome and that of the hysterical-dissociative dysmnesia, as well as between these and the psychology of normal forgetting, we will want to examine what is known, or theorized, about the substrate of the amnesic syndrome and of normal remembering and forgetting. It would be in the hope, not that precise correspondence would emerge, but that a terra firma would be established on which the data of behaviour and process could be securely placed. A psychopathology that does not take full account of related physiological and pathological neural phenomena is riskily unmoored and unballasted. But there is also a notorious danger in trying to pass from psychological to physiological and anatomical data. Lashley said that 'we seem little nearer to an understanding of the nature of memory trace than was Descartes'. It is startling, after that, to turn to what Descartes actually wrote about his understanding of the nature of the memory trace: 'When the soul wills to recall something, this volition, by causing the pineal gland to bend successively now to one side and now to another, impels the spirit towards this and that region of the brain, until they come upon the part where the traces left by the object we will to recall are found. These traces consist in the manner in which the animal spirits, owing to the paths they have taken on the presence of that object, have so modified the pores of the brain that these have acquired a greater facility than the others of being opened in that same fashion when the spirits again come towards them'. If in truth we are little nearer than Descartes was to understanding the nature of memory trace, we had better be rather cautious in our conjectures about what has happened in the brain to make memory traces as scanty and inaccessible as they are in the amnesic syndrome.

Cerebral Substrate

There is now a consensus of opinion that in the Korsakoff syndrome, as in Wernicke's encephalopathy, degenerative changes are regularly and primarily found in the pericentricular and periaqueductal grey matter, the corpora mamillaria, the dorsal medial nucleus of the thalamus and to some extent in the brain-stem and cerebellum. Essential connexions between these areas, the cornu ammonis and the cingulate cortex, have been postulated and given functional significance, on the lines which Papez (1937) and, more recently, MacLean (1958) and others have emphasized. But the discrepancies between the results of ablation in human beings and animals, and the

diverse functions which these systems are believed to subserve – motivation, emotion, memory, execution of complex sequences of action – impose caution. It seems premature to assume that because the corpora mamillaria and other rhinencephalic structures show degenerative changes in the Korsakoff state, we can therefore assign to these cell-aggregates and their connexions a direct responsibility for serving the functions of memory. Brierley (1961) in his recent review of the correspondence between neuropathological findings and defect of recent memory, concluded that there are two groups of cells, not necessarily acting in unison, which are essential for remembering – the cortical group in the hippocampi and a hypothalamic group in the mamillary bodies: and he drew attention, as others have, to the extensive pathways entering and leaving these areas and linking them to the fornix. What features of the memory function depend on the integrity of either of these areas and projections it is scarcely possible to say. Penfield (1958) is sometimes invoked in support of the view that retention and recall are located in the mesial temporal cortex. His observations are very well known but it is only fair to remark that he disavows knowing how and where the recording of memory impressions takes place: he goes no further than to say that somewhere in the brain there is a 'pathway of synaptic and ganglionic facilitations which linger on after a present experience has faded into the past' leaving a record of experience which has been activated in certain of his patients by rhythmic electrical impulses delivered to the superior and lateral surfaces of the temporal cortex: he suspects that the 'ganglionic patterns of experience' are in the hippocampi. That is probably as far as anyone might go in localizing memory, at present.

I have referred to these anatomical and physiological aspects of memory only because psychopathology, however boldly independent, has to modify its formulations whenever some clear correspondence is established between physical events and psychological events. But such clear correspondence has not yet been demonstrated and the seeker after truth is confronted by a rapidly changing array of concepts borrowed from information – theory and biology. There are curious and ironical similarities between some of the recent attempts to interpret the memory process in terms of synaptic facilitation (Burns 1958) and the speculations of Freud in 1895 on the same subject. Freud postulated two sorts of neurons – 'permeable' neurons, which subserve perception, and 'impermeable' neurons, i.e. neurons in which excitation does not pass readily across the 'contact-barriers' and which subserve memory. The latter neurons are permanently affected by an excitation, so that facilitation occurs, making their 'contact-barriers' more permeable to the spread of such excitation (Freud 1954). Interesting and ingenious as was Freud's development of this neurologizing theory, I shall not quote it further; it serves, however, as a reminder of the perennial fascination of conjectures about the substrate of normal and disturbed memory.

Hysterical Amnesia

It would seem odd for a psychiatrist to finish even a very brief talk about amnesia without a further word on hysteria. Hysterical amnesia can be such a spectacular affair, and the instances of 'multiple personality' due to it are so arresting – when well told – that it gets more attention than its frequency warrants. Out of 1,259 patients admitted between April 1959 and March 1960 to a hospital receiving psychiatric emergencies in London, 58 had the organic-amnesic syndrome, but there were only 2 patients admitted during the year because of hysterical amnesia for the details of their personal identity and experience. During the last five years only 12 such patients were admitted to the hospital in question. Gross hysterical amnesia is in fact rather a rare condition. But there is a stronger reason than rarity for dealing with it summarily in a discussion of amnesic syndromes: it hardly belongs there. It is in a sense misleading to call it amnesia, for in these people, as Henri Ey (1950) has rightly said, we are dealing not with a circumscribed disorder of memory, but with a disturbance of synthesis which engages the whole personality. The War provided crude examples of the phenomenon, less spectacular than the dramatic cases reported in the last century and again lately, but clearly demonstrating that a personality-reaction rather than an isolated amnesia was here evident. The treatment was correspondingly distinct in its aims and effect. It is true that in the organic-amnesic syndrome the characteristic disorder of memory is associated with other anomalies of mental function; it is not really an isolated amnesia and nothing more. But there is, as Korsakoff so strongly emphasized, a startling contrast between the severity of the memory deficit in this condition and the excellence of other cognitive functions, especially those concerned with the use of words. The contrasts which obtrude in the mental state of hysterical dissociation are of another order and they can be abolished.

I am sorry that this brief review is inconclusive. Experimental psychology, neurophysiology, psychiatry, neurology and neurosurgery have all been depositing offerings, large and small, towards the solution of the fascinating, perplexing problems of psychopathology which the amnesic syndrome

presents. But these contributions are still far removed from synthesis or certainty. There is enough stir and movement around the subject to make a propitious turmoil: not so lively a turmoil perhaps as Freud once made with his exploration of the arcana of forgetting, but stimulating and suggestive enough to promise real advances.

REFERENCES

Bartlett F C (1932) Remembering. Cambridge

Bonhoeffer K (1904) *Allg. Z. Psychiat.* **61**, 744

Brierley J B (1961) *Gerontol. clin.* **3**, 97

Brodmann K
(1902) *J. Psychol. Neurol., Lpz.* **1**, 225
(1904) *J. Psychol. Neurol., Lpz.* **3**, 1

Bürger-Prinz H & Kaila M (1930) *Z. ges. Neurol. Psychiat.* **124**, 553

Burns B D (1958) The Mammalian Cerebral Cortex. London

Ehrenwald H (1931) *Z. ges. Neurol. Psychiat.* **134**, 512

Ey H (1950) Les Troubles de la Mémoire. (Études Psychiatriques: Étude No 9); Paris

Flament J (1957) *Acta Neurol. belg.* **57**, 119

Franz S I (1933) Persons One and Three. A Study in Multiple Personalities. New York.

Freud S (1954) The Origins of Psychoanalysis: Project for a Scientific Psychology. London

Gantt W H & Muncie W
(1942) *Bull. Johns Hopk. Hosp.* **70**, 467

Gregor A (1909) *Mschr. Psychiat. Neurol.* **25**, 218, 330

Grünthal E (1924) *Z. ges. Neurol. Psychiat.* **92**, 255

Hartmann H (1930) *Z. ges. Neurol. Psychiat.* **126**, 496

Janet P (1898) Névroses et Idées Fixes. Paris. Vol 1, Ch 3

Köppen M & Kutzinski A (1910) Systematische Beobachtungen über die Wiedergabe kleiner Erzählungen durch Geisteskranke. Berlin

Korsakoff S S (1890) *Rev. psychol.* **21**, 669

Krauss S (1930) *Arch. ges. Psychol.* **77**, 469

Lewis A J (1953) *Mschr. Psychiat. Neurol.* **125**, 589

Lidz T (1942) *Arch. Neurol. Psychiat., Chicago* 47, 588

Lindberg B J (1946) *Acta psychiat., Kbh.* **21**, 497

MacLean P D (1958) *J. nerv. ment. Dis.* **127**, 1

Mouren P P & Felician J (1958) *Ann. méd.-psychol.* **116**, 664

Nyssen R (1957) *Acta neurol. belg.* **57**, 639

Papez J W (1937) *Arch. Neurol. Psychiat., Chicago* **38**, 725

Penfield W (1958) In: Ciba Foundation Symposium on the Neurological Basis of Behaviour. Ed. G E W Wolstenholme & M O'Connor. London; p 149

Pick A (1915) *Z. ges. Neurol. Psychiat.* **28**, 344

Rey A (1959) *Arch. Psychol., Genève* **37**, 126

Russell W R (1959) Brain, Memory, Learning. Oxford

Russell W R & Nathan P (1946) *Brain* **69**, 280

Schneider K (1912) *Z. ges. Neurol. Psychiat.* **8**, 553

Talland G A
(1958) *J. nerv. ment. Dis.* **127**, 197
(1959) *J. abnorm. (soc.) Psychol.* **59**, 10

Talland G A & Ekdahl M (1959) *J. nerv. ment. Dis.* **129**, 391

Talland G A & Miller A (1959) *J. abnorm. (soc.) Psychol.* **58**, 235

van der Horst L (1932) *Mschr. Psychiat. Neurol.* **83**, 65
(1956) *Evolut. Psychiat.* **1**, 189

Whitty C W M & Lewin W (1960) *Brain* **83**, 648

Williams M & Zangwill O L (1950) *J. ment. Sci.* **96**, 484

Woodworth R S & Schlosberg H
(1954) Experimental Psychology. London

Dr R S Allison (*Belfast*)

Chronic Amnesic Syndromes in the Elderly[1]

The type of memory loss which I shall discuss is that which occurs in elderly people as the consequence of organic brain disease. In the past fifteen years more than 200 cases have been seen in the neurological department at Belfast. In most of them impairment of memory was overshadowed by other signs of disease, such as hemiplegia and disturbances of speech and language, but in 45 it was the chief, if not the only, complaint. Among these patients there were 26 men and 19 women and the average age when they were first seen was 58 years; the youngest was 37 and the eldest 69 years. Patients were studied clinically, electroencephalographically and by contrast radiography, as required. A firm diagnosis was reached in only 30 or 66% (Table 1). Those in whom the cause remained in doubt were classified as 'presenile dementia'; this included patients in whom family history was negative, there were no focal neurological signs or evidence of cerebral atherosclerosis and in whom the appearances on lumbar encephalography were indicative of diffuse, symmetrical cortical atrophy.

Table 1
Ætiology of chronic amnesic syndromes (45 cases)

		No. of cases
'Presenile dementia'		15
Intracranial tumours		6
Meningioma	4	
Right fronto-temporal	1	
Right frontal	1	
Left frontal	1	
Right parietal	1	
Pinealoma	1	
Cyst third ventricle	1	
Other space-occupying lesions		2
Chronic subdural hæmatoma right parietal	1	
Post-traumatic aerocele right frontal	1	
Cerebral atherosclerosis		6
Post-anoxic		6
Alzheimer's or Pick's diseases		5
Post-traumatic		2
General paralysis of the insane		2
Hepatic encephalopathy		1

Of the 30 others in whom a firm diagnosis was made, 6 had intracranial tumours, 4 of these being meningiomata. Cushing & Eisenhardt (1938) noted disturbances of memory in some of their cases, especially frontally-placed tumours, but in discussing convexity meningiomas they remarked that mental symptoms were notable by their absence. Sachs (1950), however, described 8 cases of meningioma, some frontal, some parietal,

[1]Modified from an original paper read before the Harveian Society of London.

others temporal, in all of which the earliest symptoms were those of dementia. Headache was a prominent symptom in only 1 of our 4 cases of meningioma. In none was there a history of epileptiform fits and in only one was papillœdema observed. Neurological signs indicative of a focal lesion, however, could be elicited in all but one case, although they were minimal and could easily have been overlooked. Lesions involving the third ventricle are known to be associated with pronounced impairment of memory (Gamper 1928, Williams & Pennybacker 1954, Conrad & Üle 1951). The patient with a third ventricle cyst had a Korsakoff psychosis, and more general absentmindedness and drowsiness were prominent in the case of pinealoma.

Cerebral atherosclerosis accounted for 6 cases. The possibility that carotico-vertebral atheroma might lead to the development of a chronic amnesic syndrome was not considered until recent years and it is conceivable, therefore, that symptoms in some patients classified as presenile dementia may have been due to this cause. Hurwitz *et al.* (1959) have reported a case in which the mental state was most suggestive of Korsakoff's psychosis.

Anoxia was responsible for a further 6 cases, in 2 symptoms being the result of temporary cardiac arrest and in 1 of defective aeration, all 3 accidents occurring during the course of surgical operations. In another case there had been severe hæmatemesis and the 2 remaining ones were due to accidental asphyxia from carbon monoxide and electrocution respectively.

Clinical Features of Chronic Amnesic Syndromes

In considering the clinical features shown by these patients, especially in their early stage of development, the hypothesis has been adopted that their intellectual decline follows the same pattern as that seen in previously healthy subjects recovering consciousness from the post-traumatic and anoxic encephalopathies, where in certain instances the recovery of 'full' consciousness, in the sense that Symonds (1937) used the term, may be delayed for several days, weeks or months. In these states it is possible to trace different phases through which the victims pass before full consciousness is regained (Table 2). In the chronic amnesic patients the same symptoms were observed except, of course, that their order was reversed, impairment of memory, perseveration, difficulty in registration and alterations in mood being the first to attract attention.

Memory loss was often difficult to evaluate because so many denied that it was of any consequence and others, whilst admitting it, excused themselves on one ground or another. These evasions were more often encountered in patients

Table 2

Phases in recovery of consciousness in post-traumatic and anoxic patients

(*a*) *Deep coma*

(*b*) *Drowsy stupor*

(*c*) *Delirium:* Aggressive, rowdy behaviour, expansive mood. Defective grasp giving rise to bizarre actions bearing a resemblance to ideational and ideomotor apraxia. Perseveration. Inability to register fresh data and recall past events. Disorientation

(*d*) *Disorientation:* Placid, acceptant, unconcerned. Defective grasp causing constructional apractic difficulties. Perseveration. Inability to register. Memory for distant events. Disorientation

(*e*) *Full consciousness:* Mood appropriate, full grasp. No perseveration. Fully orientated. Able to register and recall past experiences

with diffuse cortical atrophy than they were with focal lesions, and especially with tumours the duration of memory impairment was shorter and its onset more easy to define. Enquiry among relatives brought out this point very clearly. In patients becoming demented it was often impossible to say when memory defects had first been noticed; they had clearly been present for a long time. Memory testing was conducted by drawing up, with the aid of a relative, a series of questions on past events in the patient's life, which he might reasonably be expected to remember, allowance being made for his social and educational level.

In only 5 patients was impairment of memory strictly confined to recent events, and 2 of these had frontally placed meningiomas. In all the others memory loss affected distant and recent events. Memories for recent events, however, were most affected. Thus, one man who had recently returned from the United States, where he had lived for some years, could recall the name of the ship (*Leviathan*) and other details of his outward journey in 1924 but had no recollection of his return passage, which had been made only a few weeks before he was examined. Good preservation of memory for distant events was sometimes seen in non-progressive post-traumatic and anoxic patients, about whom the relatives frequently commented that they seemed 'to dwell in the past' and take little or no interest in current events.

Character of Memory Defects

The character of the memory loss was not easy to analyse because in most cases multiple defects were found and it was often difficult to say which was of most significance. In general, however, four chief types of defect occurred:

(1) *Inability to recall names:* When pronounced, this was usually associated with loss of spontaneous talk, the patient remaining silent unless spoken to. The difficulty in word finding lay

chiefly with nouns and proper names. Although unable to recall these from memory, amnesic patients were surprisingly good at naming sighted objects, the act of seeing or touching an object clearly helping to stimulate recall of its name. This is a point of distinction from dysphasic patients with focal lesions involving the speech area who usually find as much difficulty in naming sighted objects as they do in naming from memory. Other differences in this respect between focal and diffuse lesions are that chronic amnesics use periphrasis and gesture to a lesser extent and that they are not so prone to develop catastrophic reactions as patients with purely focal lesions, when they fail to get the word they want (Allison 1955).

As to the nature of this naming difficulty, perseveration sometimes played a part, this being shown by their ability to give a name correctly but when asked for a second name to boggle over it and keep on repeating the first name. But in the majority the defect was amnesic in origin. That is to say, if one were to give them a word they could repeat it without difficulty, although a moment or two later they had forgotten what it was.

Non-verbal tests were used to ascertain the capacity for registration in these cases: a number of objects was displayed and then, whilst the patient looked on, they were concealed in separate hiding places. Thus, when a patient watched a comb being hidden under his pillow, a key being placed in the drawer of his bedside locker and a spoon slipped under the counterpane of his bed, he appeared to be registering, but proof of his having done so was only forthcoming when, on being invited to show where they were, he was able to do so correctly. We have been in the habit of giving this test to aphasics with focal lesions as well as to chronic amnesic patients and the results show that those with focal lesions usually have no difficulty, pointing to the place of concealment of objects without hesitation, whereas patients with diffuse cortical atrophy are often unable to do so.

(2) *Temporal amnesic defects*, or inability to arrange previous events in their correct sequence were less obvious than naming defects but could be discerned in a number of cases, in some of which they seemed to be the chief disability. One instance was a woman aged 65, a university graduate, who for years before she became ill had been a private governess. So perfect was her poise at the first interview that it was difficult to believe there could be anything seriously amiss. However, she readily admitted her difficulty in remembering and submitted willingly to tests. There was no trace of perseveration, series could be repeated forwards and backwards with ease. When asked to name some flowers she rattled off: 'wallflower, chrysanthemum, dog daisy, marguerite, hairbell, hyacinth, primrose, violet', and it was the same with anything else one asked her. Sighted objects were also named instantly. The only defects lay in her great difficulty in registration, her inability to see the point of simple pictures and in an absolute constructional apraxia. Her temporal defects in memory are illustrated by the following excerpt from a conversation in 1953:

Q. 'Miss X . . . do you recall the First Great War?'
A. 'Oh yes I do. . . . I was teaching near L . . . at the time. . . . In M . . . H . . . the girl's name was Gwendoline . . . a nice child' (she then gave the name of the family and other details).
Q. 'In what year did that war begin?'
A. 'Oh . . . let me see . . . it was sometime in 1915, or was it 1914?'
Q. 'Can you recall who was the Prime Minister at that time?'
A. 'Let me see . . . was it Churchill? . . . oh no, of course not . . . it was Ramsay MacDonald of course!'
Q. 'Then there was a Second World War. Do you remember much about it?'
A. 'Well . . . I can't recall the last war. . . . I know England is at war now . . . at least I think she is . . .'
Q. 'Who was Hitler?'
A. 'Oh yes, . . . of course I recall him . . . how stupid of me . . . what happened to him? Is he in prison or is he dead?'

More severe defects in this aspect of memory may account for the peculiar behaviour of some amnesic patients who do not know when it is time to stop work or when to begin it. One man, before admission to hospital, had been upsetting the household by rising in the early hours of the morning, dressing himself and going to the office where he arrived by six o'clock. Another, who lived in the country, first drew attention to his condition – he had a right frontal meningioma – by setting out for town one day to transact business, and only realizing on his arrival that it was a Sunday.

(3) *Loss of topographic memory or inability to remember the spatial relationships of previously well-known places* was a pronounced feature in 13 patients, all of whom turned out to have diffuse cortical atrophy, this kind of memory defect, as it happened, not being observed in any of the cases with space-occupying lesions. The tendency to get lost out of doors and be found wandering was typical. Most of these patients had difficulty even at home in remembering the situation of different rooms and often could not recall upon which side of the street they lived or in which direction lay the shops, church or cinema. One patient with Alzheimer's disease was so absent-minded that after being shown one evening to his room he got into bed the wrong way round and was discovered later with his feet on the pillow and his head at the foot of the bed.

As regards loss of sense of direction; a few patients had a vague recollection of the street they were in looking unfamiliar and it is possible that this *jamais vue* effect may have heralded a minor fit, the amnesia following which was responsible for their becoming lost. In others, however, in whom there was no evidence of epilepsy, the illusion of unfamiliarity may have been related to perseveration or inability to reorientate themselves to a fresh scene, owing to persistence of the former scene. That is to say, their loss of sense of direction may have coincided with stopping to gaze in a window or enter a shop so that when they turned around or came out their minds were so preoccupied with what they had seen that they did not know which direction to take. One man, in whom this was a prominent symptom, said that when in doubt he invariably turned to the left but investigation showed that this behaviour was not prompted by his being left-handed or by the presence of a right-sided hemianopia or visual inattention.

As regards other intellectual defects shown by these patients all had difficulty in registration and over half displayed perseveration. Ideomotor apraxia (especially difficulty in dressing) was observed in 6 and visual object agnosia in 3. Unfortunately, tests for constructional apraxia were not done in all cases, but, when they were, gross defects in this sphere were always found. Their state of orientation varied; apart from disorientation in time, which is often of little significance in hospital patients, 6 were disorientated in place, 1 for persons and 5 had difficulty in distinguishing their left hand from their right and in identifying their fingers. All those given house-drawing tests showed inability to attain correct perspective.

In none of these cases was a visual half-field defect or unilateral visual inattention demonstrable. Patients with focal parieto-occipital lesions often show these signs and have difficulty not only in selecting particular objects from among a number of other objects but in deciding which of two objects is the nearer or the further away. Many patients with diffuse cortical atrophy and topographic memory loss were tested for their inability to determine the 'nearness' and 'farness' of objects placed in their view but they were usually able to do so without difficulty. This was an unexpected result because it was thought that if a focal lesion were liable to disturb particular aspects of spatial orientation, a global cerebral affection might lead to total disruption of the function. However, a possible explanation may lie in the parallel which can be drawn between the performance of demented patients with pronounced topographic memory loss and those with marked naming difficulties, who are helped in overcoming their defect by being shown the objects they are required to name. Their difficulty is chiefly in recalling names from memory. Similarly with topographic memory loss: the more concrete the task set the patient the less apparent are his spatial difficulties.

(4) *Failure to employ memory as a 'tool'. 'Amnesic indifference':* This type of memory defect was perhaps the most common. In these patients memory loss was more apparent than real and the difficulty seemed to lie in their inability, in the absence of an appropriate stimulus, to bring retained facts back to mind. Kahn & Thompson (1934) were probably the first to refer to it when they spoke of patients having lost the ability to employ memory as a 'working tool'. At that time it was thought to be typical of presenile dementia but later French authors such as Ajuriaguerra & Rouault de la Vigne (1946) noted it in post-anoxic cases, referring to it as 'une sorte d'indifference mnesique' and Williams & Pennybacker (1954) have correlated 'not bothering' to remember with lesions of the frontal cortex.

These patients usually displayed a mood of unconcern or nonchalance, often wearing a faintly amused or tolerant expression and confabulating freely to conceal their difficulties. There was little failure in retention, the fault lying chiefly in defective registration and recall so that the overall clinical picture resembled that of the Korsakoff syndrome. There was usually difficulty in reversing series but perseveration and catastrophic reactions were uncommon. Thus, one woman when visited was invariably found reading, her husband supplying her with a selection of novels each week in the belief that they helped her 'to while away the time in hospital'. They certainly had this effect, but although willing and able to recite portions aloud, a moment later she was quite unable to recall what she had read, excusing herself by saying that it was not her type of book or that the characters in it were too dull to make recall worth while.

Another typical feature of testing memory in these cases was that, when prompted, they were often able to supply other related facts gratuitously. The following is an example: The patient, a well-educated woman of 61, had a tumour (pinealoma) invading the third ventricle. The conversation related to her childhood, between the years 1892 and 1907:

Q. 'You are old enough to remember Queen Victoria, aren't you?'
A. 'Yes, I remember her.'
Q. 'Who succeeded to the Throne after her death?'
A. '. . . was it Albert' (? perseveration) . . . (prompted: Edward VII) . . . 'Oh yes, of course, Edward VII and *Queen Alexandra of Denmark*'.

There is some similarity here to the familiar business of priming a hand pump. One may first

have to pour a little fluid down the barrel to get the water to flow. So, in seeking information from these patients it is necessary to supply some particular fact before other related facts can be recalled.

Deductions drawn from purely clinical observations may tend to oversimplify a problem, but whatever may be the physiological mechanisms involved, the clinical features of the chronic amnesic syndrome (or of presenile dementia, using the term in its broadest sense) appear capable of interpretation in at least two ways.

First, there is the classical concept of the cortex acting as a storehouse, memory loss being due to its disintegration as a source of reference and comparable in this sense to a library the shelves of which have been depleted of books. Many of the clinical features of aphasia in patients with focal lesions can be so explained, and the same may be true of other specialized forms of intellectual activity. Loss of memory in diffuse cortical atrophy has also been ascribed to it, but as has been seen in the cases described failure in retention is not always demonstrable. Indeed, in many cases, clinical observation suggests that it is registration and not retention that is primarily at fault. Although such patients may have the greatest possible difficulty in registering some fresh piece of information, once they have done so they display a curious knack of retaining it so that they may surprise the examiner months later, and long after he himself has forgotten it, by their ability to repeat it verbatim.

Second, there is the possibility that memory loss in these cases may be due to breakdown of the referral mechanism occurring at an early stage, when the cortex is still relatively intact. In favour of this is the effect of priming in stimulating recall and the frequency with which moods of unconcern or indifference are encountered in such patients.

Psychologists recognize that difficulty in recall implies some sort of interference or competition and that in health this most commonly results from emotional causes. However, one hesitates to relate amnesic indifference to the changed affect that is often seen or to accept the view that moods of unconcern are due to possible leucotomizing effects of the underlying lesions. These patients vary too much in their behaviour and performances from day to day – depending on what they are doing – to make this proposition readily acceptable, nor will it account for the rapidity with which amnesic indifference disappears after the successful removal of a tumour or subdural hæmatoma. It seems more probable that this common type of memory impairment may be due to disturbance of the physiological alerting mechanism in the brain-stem and diencephalon to which, so far as I am aware, little attention has yet been paid in the presenile dementias. Penfield believes that this centrencephalic system, as he has named it, corresponds to Hughlings Jackson's highest level of functional integration, but whether this is so or not, there is reason to relate amnesic indifference to faults in these circuits, which, as we know, are symmetrically connected with widespread areas in both cerebral cortices.

REFERENCES

de Ajuriaguerra J & Rouault de la Vigne A (1946) *Sem. Hôp. Paris* **22**, 1950
Allison R S (1955) *Geriatrics* **10**, 306
Conrad K & Üle G (1951) *Dtsch. Z. Nervenheilk.* **165**, 430
Cushing H & Eisenhardt L (1938) Meningiomas: Their Classification, Regional Behaviour, Life History and Surgical End Results. Springfield, Ill.
Gamper E (1928) *Dtsch. Z. Nervenheilk.* **102**, 122
Hurwitz L J, Groch S N, Wright I S & McDowell F H (1959) *Arch. Neurol. Psychiat., Chicago* **1**, 491
Kahn E & Thompson L J (1934) *Amer. J. Psychiat.* **13**, 937
Sachs E (1950) *J. ment. Sci.* **96**, 998
Symonds C P (1937) *Proc. R. Soc. Med.* **30**, 33
Williams M & Pennybacker J (1954) *J. Neurol. Psychiat.* **17**, 115

Dr William Gooddy (*London*) read a paper entitled **Some Observations on Retrograde Amnesia**

Joint Meeting May 4–6 1961
with the Società Italiana di Neurologia
at the Royal Society of Medicine
and at the National Hospital for
Nervous Diseases, Queen Square, London

The following papers were read:

Neurological Reactions to Poliomyelitis Vaccination: A Report of Four Cases
Dr J D Spillane (*Cardiff*)

Peculiar Clinical and Histopathological Aspects of the Early Phase of Disseminated Encephalomyelitis
Professor C L Cazzullo & Dr C Ravasini (*Milan*)

Subacute Sclerosing Encephalitis with Unilateral Involuntary Movements
Dr G Pampiglione & Dr E Stroud (*London*)

Biochemical Differences in White Matter Areas of Bovine Nervous System: Proteolipids and Phosphatidopeptides
Dr L Amaducci & Dr A Pazzagli (*Florence*)

Observations on the Use of a Cytotoxic Agent in the Treatment of Malignant Brain Tumours
Mr W J Atkinson (*Manchester*)

Prednisone in the Treatment of Acroparæsthesiæ
Dr F R Ferguson, Dr L A Liversedge & Dr C Mawdsley (*Manchester*)

L'Action de Certaines Hormones Corticostéroïdes sur le Métabolisme Protéique des Cellules Motrices de la Moelle Épinière
Professor G Gomirato, Dr G F Baggio & Dr F Sibour (*Siena*)

Upon the Physiopathology of Myoclonic Syndromes
Professor M Gozzano & Dr R Vizioli (*Rome*)

Trigeminal Neuralgia due to Extrinsic Lesions in the Posterior Fossa
Mr R Campbell Connolly (*London*)

Neurological Disturbances Following Gastric Resection
Dr R Rossini & Dr G D Cavalca (*Modena*)

Cerebral Arterial Spasm – Some Fundamental Problems
Mr John Potter (*Manchester*)
(*see* Potter J M, 1959, *Brain* **82,** 367; Potter J M, 1961, *World Neurol.* **2,** 576)

An Analogy for Retrograde Amnesia
Dr William Gooddy (*London*)

The Role of Vascular Factors in Head Injury
Dr P M Daniel & Dr S Strich (*London*)

The Token Test: A Test for Mild and Latent Receptive Aphasia
Dr E de Renzi & Dr L A Vignolo (*Milan*)

Some Problems of Cerebral Dominance Studied by Intracarotid Injection of Sodium Amytal
Dr H Terzian (*Padua*)

Disorders of Memory and Aphasia
Dr W Ritchie Russell (*Oxford*)

Parietal Symptomatology: A Survey
Professor C Ambrosetto & Dr C Gentili (*Bologna*)

Section of Surgery

President Lambert C Rogers CBE VRD FRCS

Meeting April 5 1961

Operative Treatment of Herniæ [*Abridged*]

Dr Amos R Koontz (*Baltimore, U.S.A.*) said that the recurrence rate for operations for inguinal hernia was too high, and could only be diminished by careful attention to detail. There was no such thing as *the* operation for inguinal hernia. The type of operation should be adjusted to the individual case. Catgut should not be used for suturing as it was too quickly absorbed. Silk and cotton were satisfactory and recently he had been using blue linear polyethylene with encouraging results. Fat and other extraneous tissue should be removed from the cord to reduce its bulk as it passed through the internal ring. The transversalis fascia should be sutured and the conjoint tendon approximated to Poupart's ligament after all areolar tissue has been carefully cleaned away from both structures. He only used Cooper's ligament if Poupart's ligament was frayed or otherwise unsuitable. Halsted's relaxant incision in the rectus sheath was very valuable. The results of operation for inguinal hernia in fat people were bad and in these cases he used tantalum.

(The talk was illustrated by lantern slides giving operative details.)

Mr Rodney Maingot (*London*) spoke first of the way he dealt with sliding hernias. The hernial sac with its contained bowel was exposed and freed. Redundant sac was cut away and the opening closed by a purse-string suture. The closed sac and contained bowel were then reduced together through the internal inguinal ring, which was carefully reconstructed around the cord. The transversalis fascia was sutured to the shelving edge of Poupart's ligament, and the posterior wall of the inguinal canal fortified by a lattice-type repair with floss silk. In a personal series of 64 sliding hernias, 40 on the right and 24 on the left, Mr Maingot had had no recurrences.

Incisional hernias which were capable of repair by simple anatomical reconstruction presented no problem. For incisional hernias with a large gap he recommended his 'keel' operation. The stretched overlying skin and scar tissue were widely excised, and the flaps dissected well back to expose healthy abdominal wall. Care was taken not to open the peritoneum, and the whole procedure was extraperitoneal. The fibro-aponeurotic margins of the hernia were defined, cleared of fatty tissue, and approximated by interrupted sutures of floss silk. The approximated edge was then inverted with a continuous suture. Occasionally, relaxation incisions might be required in the aponeurosis, especially with large epigastric hernias. Out of 81 cases in which he had performed this operation, there were 6 recurrences, 4 of which were small and readily corrected by a further minor procedure. Another was reoperated on by a further 'keel' procedure, and the patient was free of recurrence three years after the second operation.

Mr W J Lytle (*Sheffield*)

Anatomy and Function in Hernia Repair

The Internal Inguinal Ring

The internal or deep inguinal ring is a U-shaped fascial structure with attachments to the transversus abdominis muscle which give it mobility and protect the opening against the onset of a hernia. The ring in its natural shape can only be seen if the pelvic bones are present. The bony framework of the pelvis holds the abdominal muscles and transversalis fascia in place and if the pelvic bones are missing the ring falls away and disappears from view. The internal ring has received little recognition from anatomists because they have not realized that it can only be seen in anatomical specimens when the bones of the pelvis are present. Surgeons who are not aware that the ring must be exposed and secured before the sac is tied off have also failed to find it at operations.

Fig 1 *Photograph of the posterior aspect of the lower half of the anterior abdominal wall showing, on the right side, the U-shaped internal ring*

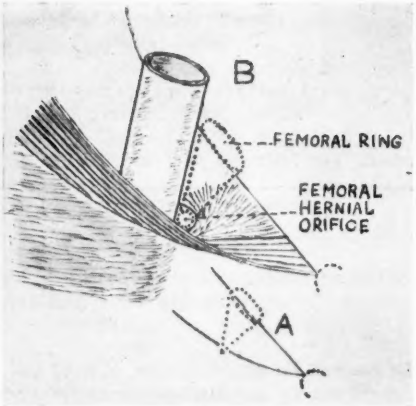


Fig 2 *Diagram A shows in dotted lines the intact femoral canal and B the canal breached by a femoral hernia. The curved edge of Gimbernat's ligament lies at the femoral hernial orifice*

Fig 1 shows the posterior aspect of the lower half of the anterior abdominal wall in its bony setting. The peritoneum has been removed to expose the transversalis fascia. The spermatic cord held in artery forceps in seen disappearing through the right internal ring. The U-shaped ring composed of thickened transversalis fascia has two pillars which are attached above to the transversus abdominis muscle. The attachments of the pillars are important. The medial or inner and stronger pillar is attached to the aponeurosis of the transversus muscle and then passes round to join the arcuate line. The lateral or outer and weaker pillar is attached to the muscular as well as the aponeurotic fibres of the transversus muscle. The muscle fibres of the transversus abdominis lie obliquely in the lower part of the abdominal wall and when this muscle contracts vigorously (Lytle 1945) the ring which is attached to it is pulled upwards and laterally to close around the spermatic cord. This active closure mechanism of the ring can be seen at hernia operations performed under local anæsthesia. (A film to demonstrate this was presented.)

The movement of the internal ring is explained as follows: When there is any attempt at protrusion of the abdominal contents through the ring, as in acts of coughing or straining, the pillars of the ring are at once pulled upon and this pull is transmitted to the fibres of the transversus abdominis muscle. The transversus muscle contracts with the other muscles of the anterior abdominal wall during coughing or straining. If, during contraction, tension is applied to the transversus muscle by the pillars of the ring, the contraction is greatly increased and the ring is pulled upwards and outwards around the emerging spermatic cord. This action is an example of the stretch reflex of Liddell and Sherrington who showed that when a muscle is caused to contract a stretch applied to it enhances its contraction to a considerable degree.

Repair for Oblique Inguinal Hernia

In oblique hernia the internal ring becomes enlarged as the hernia increases in size. As the ring possesses this remarkable closure mechanism it must be reduced to normal size to enable it to act efficiently.

The chief difficulty is to find the internal ring at operations, for if the routine method of removing the sac is followed, the ring with the stump of the sac retracts back into the abdomen and disappears from view. When the hernial sac has been dissected free from the cord, the ring can, however, be brought into full view by pressing it forward with the index finger which has been passed through the neck of the opened sac. The ring edge is then easily secured in artery forceps and its medial and lateral pillars are separated from the neck of the sac and from the spermatic cord. To expose, secure and separate the ring margins in this way, is the most important step in the operation. The sac is then tied and removed and the edges of the ring are stitched together, starting medially and working laterally until the ring fits snugly around the cord. This operation was originally described by Marcy (1892).

The outer or lateral pillar of the ring is often found to be weak and the repair should then be modified. In such cases the mobility of the ring has to be sacrificed and the medial or inner pillar is sutured to the inguinal ligament or to the upper margin of the deep femoral arch, a description of which is given below.

Repair for Direct Inguinal Hernia

The simplest and probably the most successful method of repair in direct hernia is suture of the cut edge of the aponeurosis of the transversus muscle to the edge of the inguinal ligament.

There are some details of the anatomy of the posterior wall of the inguinal canal which merit attention, for this wall is not usually closely examined at operations for oblique hernia, while in direct hernia when the posterior wall is in full view the anatomy is defective. There is a general impression that the posterior wall of the inguinal canal is composed of transversalis fascia only, when in fact there is an important supporting layer in front of it. In the lower half of the wall lies a strong band of transverse fibres which stretches across and gives support to the transversalis fascia behind it. This ligament, the deep femoral arch, is attached below to the inguinal ligament but is not readily seen until the lower leaf of the cut cremaster is retracted downwards and the areolar tissue on the surface of the arch is wiped off. The deep femoral arch is usually about 1 cm in breadth and from its upper edge emerge the cremaster vessels and the genital branch of the genito-femoral nerve. These vessels should be recognized for they arise from the inferior or deep epigastric vessels and may bleed if roughly handled. It is advisable to tie and remove the cremaster vessels together with the lower leaf of the cremaster muscle to give a clear field in the repair of direct inguinal hernia. The upper margin of the deep femoral arch lies just below the internal ring and when the lateral pillar of the ring is weak the strong medial pillar can be usefully stitched to the deep femoral arch in repair of an oblique hernia. In direct hernia the arch, often of poor quality, is of little value in repair.

I would make a plea to discard the name 'conjoint tendon' and refer separately to the internal oblique muscle and to the aponeurosis of the transversus abdominis muscle. The expression 'conjoint tendon' with such variable meaning, has been responsible for much confusion in the surgery of hernia.

Femoral Hernia: Anatomy and Repair

I hold unorthodox views (Lytle 1957) on the anatomy of the femoral canal.

We would all agree that the femoral canal is a funnel-shaped cavity about 1·5 cm long. At the upper end is the femoral or crural ring which lies at the level of the ilio-pectineal line. The lower end of the canal ends blindly at the level of the inguinal ligament (Fig 2).

When a femoral hernia is present this blind lower end of the canal is breached and a new opening comes into existence. This new opening is the essential defect in femoral hernia for unless it is present a femoral hernia does not exist. If this lower opening is important it should surely have a name and I have named it 'the femoral hernial orifice'. In femoral hernia there are therefore two separate openings, the femoral ring above, and the femoral hernial orifice below, and these openings are widely different.

The femoral hernial orifice lies at the lower end of the femoral canal at the level of the inguinal ligament and lies half an inch below the ileopectineal line. The orifice is round, usually much smaller than the femoral ring and has a strong fibrous edge with no bony relations. The femoral hernial orifice is the opening which presents when one is operating on a femoral hernia from below and is also the ring round the neck of the sac and the ring which causes strangulation. Finally, the femoral hernial orifice is the opening which has Gimbernat's ligament as its inner boundary.

We have always been taught that Gimbernat's ligament lies at the upper end of the femoral canal, yet in practice we infer that the ligament lies at the lower end when we incise it at this point to relieve a strangulated hernia. The confusion arises because it has not been realised that Gimbernat's ligament is composed of two parts, the tendinous and the fascial (Fig 2). The tendinous part is derived from the inguinal ligament, with a straight inner edge which we see when operating on inguinal hernia. The deeper or fascial part derived from the fascia lata lies hidden behind the inguinal canal. This deep part is attached in the main to the ilio-pectineal line but its curved outer edge is slung to the pectineal fascia half an inch below this line where it forms the inner boundary of the lower opening, the femoral hernial orifice.

The usual repair for femoral hernia is to close the femoral ring which normally lies open, by such well-recognized operations as Lotheissen's, Cheatle's, Henry's or McEvedy's, but if we believe that Gimbernat's ligament lies at and reinforces the lower opening, it would seem preferable to close the femoral hernial orifice instead by a purse-string suture.

Principles of Hernia Repair

There are four principles or aims which I suggest should be followed in hernia repair:

(1) The operation should aim to restore the inguinal or femoral canal to normal. This is achieved in inguinal hernia by repair of the internal ring or by suture of the cut edge of the transversus aponeurosis to the inguinal ligament and in femoral hernia by closing the femoral hernial orifice.

Cooper's ligament repair or Lotheissen's operation distorts the posterior wall of the

inguinal canal. The plane of the posterior wall of the inguinal canal is downwards to the back of the inguinal ligament and to the most medial end of the ilio-pectineal line. In the interval or space between the attachment of the transversus aponeurosis to the inner end of the ilio-pectineal line and the femoral vein, the posterior wall passes down to the back of the inguinal ligament and then turns back to its attachment to the ilio-pectineal line. To stitch the cut edge of the transversus aponeurosis directly to Cooper's ligament drags the posterior wall backwards out of its normal alignment and brings the suture line under marked tension.

(2) White fibrous tissue or tendon should be joined to similar tissue for this gives the strongest repair. Koontz (1926) has shown that cut muscle does unite to fascia but as the amount of fibrous tissue in muscle is limited, union is correspondingly weaker.

(3) Only cut or raw edges should be joined together for these give the maximum release of fibroblasts. The inguinal ligament is not a cut edge but when the cremaster muscle is removed the white fibres which join it to the inguinal ligament are severed and a raw edge results.

(4) Muscle, fat and areolar tissue must not intervene at the line of union. When the cut edge of the transversus aponeurosis is stitched to the inguinal ligament care should be taken that the muscle fibres of the internal oblique do not intervene and that extraperitoneal fat does not get in the way. Koontz (1926) has shown that areolar tissue is a barrier to fibrous union. Prior to suture the shining fibres of the inguinal ligament or the deep femoral arch should be exposed by wiping away the areolar tissue on their surfaces.

REFERENCES
Koontz A R (1926) *Surg. Gynec. Obstet.* **42**, 222
Lytle W J
(1945) *Brit. J. Surg.* **32**, 441
(1957) *Ann. R. Coll. Surg. Engl.* **21**, 244
Marcy H O (1892) The Anatomy and Surgical Treatment of Hernia. New York

Mr R E Isaac (*Aberystwyth*) stressed the importance of the variations in the attachment of the conjoint tendon to the ilio-pectineal line. In large hernias, the ilio-pectineal line could easily be palpated in the recumbent patient through the external ring and the degree of attachment of the conjoint tendon ascertained. If this attachment is absent or deficient, the conjoint tendon must be sutured down to Cooper's ligament with the aid of a relaxant incision.

Meeting May 5 and 6 1961
at the Maternity Hospital Cardiff

Paper

The Parathyroids after Thyroidectomy

Unsuspected Partial Hypoparathyroidism following Thyroidectomy [*Summary*]

by R Harvard Davis BM (*Cardiff*)

In 1936 Kramer suggested that there might be a condition of partial hypoparathyroidism with mild symptoms and a normal plasma calcium. Previous estimates of the incidence of hypoparathyroidism following thyroidectomy have varied between 0·5% and 4%, and are probably inaccurate because the definition of hypoparathyroidism has been vague. Tetany is not synonymous with hypoparathyroidism nor is the plasma calcium a reliable indication of parathyroid function. A satisfactory definition of hypoparathyroidism, in keeping with the known experimental facts (Patt & Luckhardt 1942), is that the condition is present if the parathyroid glands are unable to maintain the plasma calcium when efforts are made to reduce it artificially.

The total population in the survey consisted of two parts: My own patients (the Cardiff group numbering 46) and those in a defined area in the Vale of Glamorgan, making a total of 80 patients. All these thyroidectomy patients were visited and a specimen of their blood obtained. For practical reasons it was not possible to follow up the patients in the Vale of Glamorgan, and the figure for the incidence of partial hypoparathyroidism is drawn from the Cardiff group only. Blood was also obtained from 82 normal persons selected by a random process from the population of the Rhondda Fach in Glamorgan.

Fig 1 shows the frequency distribution of the plasma calcium values of these two groups. The mean values differ significantly, but more important is the difference in the distribution of the values. Only 10% of the control group had plasma-calcium values of less than 9·3 mg/100 ml, whereas 34% of the thyroidectomy group had a value less than 9·3 mg/100 ml.

Table 1 shows the symptoms complained of by the thyroidectomy subjects when they were inter-

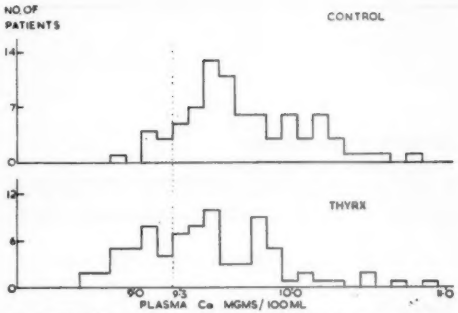


Fig 1 *The frequency distribution of the plasma calcium values in 82 control (top) and 80 thyroidectomy patients (bottom)*

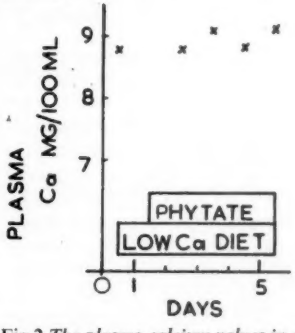


Fig 2 *The plasma calcium values in a normal thyroidectomy subject during the calcium deprivation test*

viewed, and the progressive increase in the frequency of the symptoms with a lower plasma calcium is well demonstrated.

The patients with a plasma calcium at the lower limit of normal were submitted to the calcium deprivation test (Smith *et al.* 1960). The response to this test in a normal person is shown in Fig 2, whilst the response in a case of partial post-operative hypoparathyroidism is shown in Fig 3.

This survey of patients in Glamorgan who had had a thyroidectomy reveals a high incidence of plasma calcium values in the lower range of normal. Calcium deprivation shows that, in many

Table 1

Symptoms in 80 thyroidectomy subjects grouped according to the plasma Ca found in the survey

Symptom	*Plasma Ca*		
	9·3 mg%	*9·3–9·8 mg%*	*9·8 mg%*
Headache	19%	3%	4%
Abdominal pain	27%	16%	9%
Ectodermal lesions	50%	36%	22%
Lethargy	42%	19%	17%
Dysphagia	4%	–	–
Mental symptoms	66%	51%	35%
Paræsthesiæ	42%	36%	22%
Tetany	4%	–	–
Relationship of symptoms to menses	27%	29%	9%

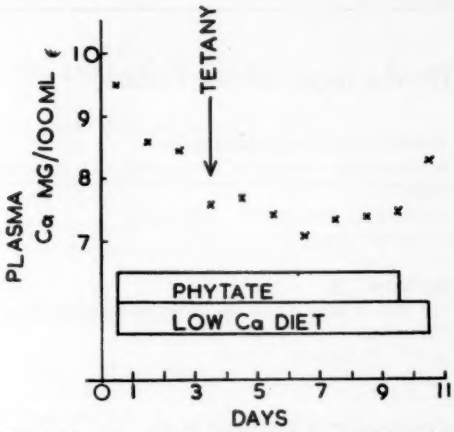


Fig 3 *The plasma calcium values in a patient with partial post-operative hypoparathyroidism during the calcium deprivation test*

instances, these low values were associated with diminished parathyroid function: thus 26 of the 46 Cardiff patients had a plasma calcium of 9·5 mg/100 ml or less. Of these, 17 were tested, and 11 or 24% of the Cardiff patients with thyroidectomy had an abnormal response showing insufficiency of the parathyroid glands. All except 2 of these 11 patients had symptoms of varying severity which caused considerable incapacity.

Note: The investigation described here in brief was undertaken by the author in collaboration with Dr Paul Fourman and Dr J W G Smith of the Medical Unit, Cardiff Royal Infirmary. It illustrates the benefit that can be obtained by collaboration of a general practitioner with a clinical research unit. The work is being published in greater detail in the *Journal of Clinical Endocrinology and Metabolism.*

REFERENCES

Kramer P H (1936) *Ned. Tijdschr. Geneesk.* **30, 3008**
Patt H M & Luckhardt A M (1942) *Endocrinology* **31, 384**
Smith J W G, Davis R H & Fourman P (1960) *Lancet* **ii, 510**

Provost A Trevor Jones gave a lecture entitled **The New Teaching Hospital for Wales**

The following short papers were also read:

Experimental Air Embolism
Mr H Harley
The Action of X-rays on Carcinoma
Professor C A Pannett
Hypoparathyroidism following Thyroidectomy
Mr J S H Wade
Surgery of the Vertebral Bodies
Mr Harold J Richards

Books received for review

Achelis J D & von Ditfurth H eds
Befinden und Verhalten: 'Starnberger Gesprache 1960'
pp iv+110 illustrated DM 14.80
Stuttgart: Georg Thieme 1961

Bannister C R
The use of drawing in the study of anatomy and physiology
pp 37 illustrated 17s 6d
Edinburgh and London: E & S Livingstone 1961

Caldeyro-Barcia R & Heller H eds
Oxytocin
pp xxiv+443 illustrated £5
Oxford, &c: Pergamon Press 1961

Ciba Foundation Symposium
Somatic stability in the newly born
edited by Wolstenholme G E W & O'Connor M
pp xii+393 illustrated 50s
London: Churchill 1961

Ciba Foundation Study Group No. 8
Problems of pulmonary circulation
edited by de Reuck A V S & O'Connor M
pp viii+96 illustrated 12s 6d
London: Churchill 1961

Ciba Foundation Study Group No. 9
Progesterone and the defence mechanism of pregnancy
edited by Wolstenholme G E W & Cameron M P
pp viii+108 illustrated 12s 6d
London: Churchill 1961

Hamburger J ed
Actualités néphrologiques de l'Hôpital Necker 1961
pp 320 illustrated NF 58,50
Paris: Éditions Médicales Flammarion 1961

Hausman L
Illustrations of the nervous system (Atlas III)
pp xxxi+168 illustrated 76s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

Heron A & Chown S M
Ageing and the semi-skilled
A survey in manufacturing industry on Merseyside
Medical Research Council Memorandum No. 40
pp viii+59 5s
London: Her Majesty's Stationery Office 1961

Kimler A
Manual of clinical bacteriology
pp xiii+201 illustrated 38s
Philadelphia and Montreal: J B Lippincott
London: Pitman 1961

Kraus H & Raab W
Hypokinetic disease
Diseases produced by lack of exercise
pp ix+193 illustrated 60s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

Mercer E H
Cells and cell structure
pp 100 illustrated 12s 6d
London: Hutchinson Educational 1961

Recordier A M, Mouren P & Serratrice G
Les ostéo-arthropathies nerveuses
pp 167 illustrated NF 28
Paris: Expansion Scientifique Française 1961

Schettler G ed
Arteriosklerose, Ätiologie, Pathologie, Klinik und Therapie
pp xvi+728 illustrated DM 98
Stuttgart: Georg Thieme 1961

Sinclair D
A student's guide to anatomy
pp ix+91 illustrated 7s 6d
Oxford: Blackwell Scientific Publications 1961

Woolmer R
The conquest of pain
pp 171 illustrated 18s
London: Cassell 1961

Section of Medicine

President E R Cullinan MD

Meeting April 25 1961
at St Bartholomew's Hospital London

Short Papers

Arteriosclerosis in Wild Animals in Captivity [*Abstract*]

by R Finlayson MD and
C Symons MD MRCP (*London*)

A study has been made of the arterial lesions occurring in captive animals. The specimens were obtained at post-mortem from 366 birds, 185 mammals and 69 reptiles. The majority of specimens were obtained from animals that died in the London Zoological Gardens; a few specimens were received from private individuals. The heart and attached vessels, sometimes including the complete aortæ and branch arteries, were examined macroscopically and histologically. Lipid-containing areas in arteries were picked out by staining with Sudan IV in the gross specimen and by suitable fat stains in microscopic sections. Lesions were divided into two groups: (1) Those containing lipid. (2) A mixed group which included focal intimal thickenings without lipid deposition; medial degeneration and calcific lesions of the media and the various forms of arteritis. The first group was further divided into lesions in which fatty streaking was the only change and others in which atherosclerotic plaque formation was present.

Fatty streaking was found in 21% of birds, 21% of mammals and in only 2% of reptiles. Atherosclerotic changes were present in an additional 19% of birds, 3% of mammals and one reptile only. Fatty streaking thus occurred as frequently in birds as in mammals but the atherosclerotic lesion was considerably more common in birds. This may have been a reflection of the age grouping of the species, as the birds tended to be older whilst many of the mammals died young. The earliest accumulations of lipid were usually present as small irregular patches at the junction of the aorta and its large branches; the larger atheromatous lesions were found as commonly in the thoracic aorta as in the abdominal segment. Variations in the histological detail of plaques were observed in specimens from different animals and, in some instances, from the same animal. The lipid present was usually of two types: sudanophilic droplets and non-sudanophilic, anisotropic crystals with the staining properties of 'cholesterol'. The lesions did not progress to local ulceration, and mural and occlusive thrombus formation was extremely uncommon. Atherosclerosis was rarely found in the coronary arteries.

Further studies are in progress to extend our knowledge of arterial disease in animals and a survey is being made in an attempt to relate diet, age, stress and blood lipid levels to the lesions of atherosclerosis.

This work has been done in collaboration with Mr R N T-W-Fiennes and we are indebted to him and others for help.

Five Cases of Syphilitic Hepar Lobatum with Portal Obstruction

by Gabor Gencsi MD[1] (for Alan Hunt MCh)

In each of these 5 syphilitic patients with portal hypertension the liver was found at laparotomy to be coarsely and irregularly lobulated, showing an appearance which has been described as 'hepar lobatum', a grotesque deformity characteristically resulting from tertiary syphilis.

Case 1 Male, aged 53 (Dr C S Nicol's case, Nicol & Terry 1951, Nicol 1952)
1944: Hæmatemesis. 1946: Liver and spleen found to be enlarged. 1947: The abdomen began to swell and paracentesis for his ascites was necessary. He was thought to be a case of Laennec's cirrhosis, and medical therapy for this disease was started. As there was no improvement and because the serological tests for syphilis were positive, penicillin therapy was begun (21.11.47); forty-eight hours later diuresis com-

[1]From Santo Antonio Hospital, Oporto, Portugal; British Council Scholar at St Bartholomew's Hospital, London

menced, reaching a maximum of 4·45 l. on the ninth day. Ascites and œdema disappeared by the fourteenth day.
8.3.48: Symptom free.
2.3.50: Acute appendicitis; appendicectomy. No ascites; liver grossly enlarged, with the appearance of 'hepar lobatum'. Portal pressure 260 mm water.
December 1960: The patient was seen, aged 69, in very good condition, leading a busy life and at full work.

Case 2 Female, aged 54
In good general health until November 1954 when her abdomen began to swell. Paracentesis at another hospital; microscopic study of the fluid suggested a diagnosis of malignant disease of the ovaries. 9.12.54: Transferred to Royal Marsden Hospital for intraperitoneal injection of radioactive gold and pituitary irradiation.

On admission: Very ill and emaciated; gross ascites, large lobulated epigastric mass. W.R. and Kahn tests positive. Other laboratory findings normal.

Laparotomy: (1.2.55): No evidence of pelvic tumour found. Splenomegaly; liver enlarged with typical appearance of 'hepar lobatum'. Portal venous pressure 220 mm water. Biopsy of liver showed gummatous foci.

A course of bismuth oxychloride and penicillin was given on Dr C S Nicol's advice.

The patient's condition improved, but as ascites persisted, a second laparotomy was carried out at St Bartholomew's Hospital in May 1955. The previous finding of hepar lobatum was confirmed. Since a portal venogram showed almost complete thrombosis of the portal vein, an end-to-end spleno-renal anastomosis was constructed. The portal pressure, which before the operation had been 280 mm water, dropped to 180 mm. The patient made a good recovery, gained weight and strength and returned to full work. Six years later, she is well and at full work, and has also survived a Wertheim's hysterectomy for carcinoma of the cervix.

Case 3 Male, aged 58. Referred by Dr G E Hosking
6.10.58: Admitted to Royal Marsden Hospital.
History: 1941: Jaundice after immersion in icy sea while on Arctic convoy to Russia. Laparotomy revealed a much enlarged lobulated liver. Between 1942 and 1946 he developed ascites which required paracentesis. In 1947 and 1949 he had a hæmatemesis and a melæna and in 1952 and 1958 he had further attacks of melæna. All these bleeding episodes required blood transfusions.

On admission: A healthy-looking man with a slightly enlarged liver, splenomegaly and loss of pain sensation in the testes. Barium swallow showed varices. W.R. and Kahn tests positive. Other laboratory findings normal. The patient was given an intensive course of antisyphilitic treatment. At operation in October 1958 his liver was found to be grossly deformed, with a smooth surface on which numerous white plaques could be seen. Portal venography outlined the portal vein, left gastric vein and the varices of the lower œsophagus and fundus of the stomach. An end-to-side porta-caval anastomosis was constructed, and the portal pressure dropped from 250 to 150 mm water. When seen in December 1960, his condition was good. He had had no further hæmorrhage, had no ascites and was at full work.

Case 4 Female, aged 68
15.12.60: Admitted to Royal Marsden Hospital having been ill for two months following hæmatemesis.

On admission: Pale and anxious, abdomen slightly distended. The liver and spleen were easily felt. Barium swallow showed well-marked varices in the œsophagus and in the fundus of the stomach. W.R. and Kahn tests positive. Other laboratory findings normal.

Past history: In 1957 she had been treated by Mr W A Mill for a gumma of the palate. W.R. and Kahn tests were positive and the diagnosis had been confirmed microscopically. Following antisyphilitic treatment the lesions in the palate had healed.

With the diagnosis of portal hypertension probably caused by syphilitic lesions of the liver, operation was advised (January 1961). A lobulated right lobe of the liver was found, with a healed calcified lesion separating it from a relatively normal left lobe. As the portal venogram showed a thrombosed portal vein, an end-to-side spleno-renal anastomosis was constructed. Portal pressure dropped from 360 to 280 mm water. Biopsy of the liver showed a syphilitic gumma with patchy calcification. The patient made an excellent recovery and was discharged five weeks after the operation. She has now fully recovered.

Case 5 Male, aged 63
In good general health until September 1960 when he had a large hæmatemesis. At operation elsewhere hepatomegaly and splenomegaly suggested portal hypertension.

On admission to St Bartholomew's Hospital: A small man, deaf, with the liver just palpable and without ascites. Barium swallow disclosed small varices at the lower third of the œsophagus. W.R. and Kahn tests positive. Other laboratory findings normal.

Past history: Jaundiced for six months in 1915. He had had a course of antisyphilitic treatment and was a heavy drinker. A provisional diagnosis of portal hypertension due to Laennec's cirrhosis was made but the alternative of syphilitic disease of the liver was considered. At operation (October 1960) the liver was markedly scarred and fibrosed, with patchy calcification. A large cirsoid aneurysm of the splenic artery and two small saccular aortic aneurysms were seen. Portal venography showed an obliterated portal vein and a tortuous splenic cavernoma. The spleen was removed, causing the portal pressure to drop from 220 to 60 mm water. During convalescence the patient developed hepatic coma. He recovered from one episode only to die three months after operation of liver failure. At autopsy it was found that he had a primary carcinoma within the lobulated cirrhotic liver.

Discussion

In all these patients, operated on during the last eleven years, syphilitic disease of the liver as the probable cause of portal hypertension had been considered before operation.

In 4 of them this cause was definitely established. In the fifth patient, the primary carcinoma of liver may have contributed to the portal obstruction. But the size of the cavernoma suggests that portal hypertension and stagnation had been present for many years, presumably the result of gummatous hepatitis.

These very deformed and distorted livers show surprisingly good function. Hahn (1943), in his review of syphilis of the liver, noted this and offered the following explanation: 'The most outstanding characteristic of tertiary syphilis of the liver is the focal nature of the process. In an organ with the functional reserve and capacity of regeneration of the liver, manifestations of hepatic insufficiency can rarely be expected.' The second interesting point is the frequency of portal vein thrombosis. Its pathogenesis still remains uncertain (Hunt 1956, Moschcowitz 1959), but there is evidence here that thrombosis must be regarded as the addition of an extrahepatic obstruction to an already congested, turgid and static portal tree. Thirdly, in two of these cases calcification was present in the liver. There is no ready explanation for how and why it occurs (Alergant 1956, Marc 1960) except that it may be evidence of healed gummatous inflammation.

We must still be constantly aware of the possibility of syphilitic disease of the liver being a cause of intrahepatic portal obstruction.

REFERENCES
Alergant C D (1956) *Arch. intern. Med.* **98**, 340
Hahn R D (1943) *Amer. J. Syph.* **27**, 529
Hunt A H (1956) *Brit. J. clin. Pract.* **10**, 89
Marc R (1960) *J. Radiol. Electrol.* **41**, 481
Moschcowitz E (1959) *Arch. Path., Chicago* **68**, 180
Nicol C S (1952) *Med. ill.* **6**, 394
Nicol C S & Terry R B (1951) *Brit. J. vener. Dis.* **27**, 20

The following papers were also read:

Air Pollution and Disease
Dr P J Lawther

Hyperoxaluria
Dr R W E Watts (for Professor E F Scowen)

Serial Electrocardiograms and Serum Lipoproteins in Symptomless Men
Dr D Weitzman and Dr E Smith

Meeting May 30 1961

Chronic Lung Disease [*Abridged*]

Dr Louis E Siltzbach (*New York*)

Investigation of Chronic Lung Disease

I am presenting several ancillary diagnostic techniques which the physician can use for the investigation of lung disease. These techniques are intended to supplement, but not to replace, the usual forms of investigation. They are simple and relatively innocuous.

In Table 1 are listed those now in fairly common use. Most of them are aimed at establishing a tissue diagnosis by biopsy or by cytologic studies. Some depend upon the patient's reactivity to a specific intradermal test. Others are biochemical studies directed at uncovering abnormalities associated with some chronic lung diseases.

Open lung biopsy: By this technique a definitive diagnosis can be obtained in more than 80% of cases of obscure disseminated lung conditions. The method has been slightly modified since it was first introduced by Klassen *et al.* (1949). Most surgeons prefer local anæsthesia.

Through a small intercostal incision, a small lappet of lung is delivered by applying positive pressure to a face mask. The extruded edge of the lung is clamped and excised; and the lung is sutured. A water-sealed catheter may be left in for twenty-four to forty-eight hours. Complications are uncommon. The only contraindication is the presence of a bleeding tendency.

Apart from histological examination the specimen may be sent for culture and special stains to detect bacteria or fungi, as well as for chemical, spectrographic and X-ray diffraction analyses.

Open thoracotomy: A second more familiar diagnostic procedure is exploratory thoracotomy under general anæsthesia. Mass chest roentgen surveys often disclose solitary nodules in the periphery of the lung among asymptomatic patients. When no substantial amount of calcium can be demonstrated by tomography, it may be very difficult to differentiate an early lung carcinoma from a granuloma or a hamartoma. Recently, the Gomori methenamine-silver tissue stain has enabled pathologists to identify fungi, mainly *Histoplasma capsulatum* and *Coccidioides immitis*, in granulomas in about 75% of instances

Table 1
Ancillary investigations of chronic lung disease

Investigation	*Diseases where applicable*
1 Open lung biopsy (Klassen *et al.* 1949) (local anæsthesia)	Diffuse lung diseases: sarcoidosis, Hamman-Rich syndrome, honeycomb lung, histiocytoses, pneumoconiosis, beryllium disease
2 Open thoracotomy (general anæsthesia)	Localized nodule: tuberculoma, histoplasmoma, benign or malignant neoplasm
3 Scalene node biopsy (Daniels 1949) (local anæsthesia)	Diffuse or localized lung disease with mediastinal adenopathy; sarcoidosis, carcinoma, tuberculosis, Hodgkin's disease
4 Pleural needle biopsy (open biopsy if needle biopsy fails) (local anæsthesia)	Tuberculous or carcinomatous pleural effusion or pleural 'scalloping' (localized pleural neoplastic deposits)
5 Paracarinal biopsy *via* bronchoscopy (Rabin *et al.* 1952)	Carcinoma of major bronchus, assessing whether operable
6 Random biopsies of muscle, bronchial and nasal mucosa, region of old scars (Löfgren *et al.* 1955)	Sarcoidosis
7 Cytologic examination: sputum, bronchial washings, pleural fluid	Malignancy of lung and pleura
8 Intradermal tests: tuberculin, histoplasmin, coccidioidin, blastomycin (read at 48–72 hours)	Tuberculosis and fungal diseases
Kveim, lepromin and beryllium patch test (read at 4 weeks with biopsy of test site)	Sarcoidosis, tuberculoid leprosy, beryllium disease
9 Biochemical studies: blood, urine, sweat	
Hypercalcæmia, hypercalciuria	Sarcoidosis, beryllium disease, neoplasms
Hyperglobulinæmia	Sarcoidosis, Hamman-Rich syndrome
Hypogammaglobulinæmia	Repeated bacterial pneumonias
Elevated Na+, Cl− in sweat, pancreatic enzyme deficiency	Cystic fibrosis of pancreas (mucoviscidosis)
Elevated lactic dehydrogenase	Pulmonary infarction
Elevated blood serotonin and 5-HIAA urine levels	Bronchial adenoma (carcinoid) with or without metastasis

(Hutcheson & Waldorf 1960). By similar methods, fungi have also been identified within broncholiths removed bronchoscopically (Weed & Andersen 1960). The stones which represent calcified lymph nodes eroding through the bronchial wall and causing inflammatory strictures usually stem from an obsolete tuberculous infection. In the midwest United States, where histoplasmosis is a more common cause of mediastinal lymph node calcification than tuberculosis, the fungi are now being identified within broncholiths as well.

Scalene node biopsy: Daniels (1949) used this procedure primarily to determine whether a carcinoma of the lung had spread into the lymphatics beyond the thorax. Its greatest use, however, is in the diagnosis of early sarcoidosis. Carstensen (1954) found the characteristic non-caseating granuloma in 60% of 200 patients in whom the presence of sarcoidosis was strongly suspected. On occasion, tuberculosis and silicosis may be discovered by this means when they involve the lymph nodes of the fat pad.

Pleural needle biopsy: Aspiration biopsy of the parietal pleura by Vim-Silverman needle, like aspiration biopsy of the liver and kidney, is a simple and useful technique. In the presence of an idiopathic pleural exudate, a specific diagnosis can be obtained by this means in more than half the patients (Donohoe *et al.* 1957, Mestitz *et al.* 1958). Fragments of pleural tissue adequate for histologic examination are obtained in three of every four attempts.

Among young adults, pleural tuberculosis is the most common condition diagnosed by this method, but in older patients carcinomatous invasion of the pleura is more often discovered.

When pleural thickening without fluid is present, the technique is less satisfactory.

Paracarinal biopsy via *bronchoscopy:* The paracarinal biopsy technique is not primarily a diagnostic procedure; its object is to assess whether a lung carcinoma is operable. It is employed when a bronchogenic carcinoma is visible through a bronchoscope and is at some distance from the carina. A bronchoscopic biopsy of the main bronchus on the side of the carcinoma is performed 1 cm or less beyond the bifurcation of the trachea. Beneath an apparently normal mucosa in this region, tumour cells may be found in the submucous lymphatics in one of every six cases studied (Rabin *et al.* 1952).

Since the surgeon is required to leave a bronchial stump of at least 1 cm in length when he performs a pneumonectomy, the presence of paracarinal spread of tumour contraindicates the operation. Involvement is more common with carcinoma of the right lung than of the left.

Random biopsies of muscle, bronchial and nasal mucosa, old scars: The diagnosis of sarcoidosis can sometimes be supported by finding characteristic histological changes in a muscle biopsy (usually deltoid or calf muscle), in biopsy of bronchial and nasal mucosa, or by examination of a nodular deposit in a scar (Löfgren *et al.* 1955).

Cytologic examination: sputum, secretions by bronchoscopy, pleural fluid: One of the principal obstacles to early diagnosis of a central carcinoma of the lung is the lack of abnormal roentgen findings in the chest until the carcinoma becomes fairly advanced.

Experienced cytologists can now find exfoliated carcinoma cells in sputum and bronchial washings when the bronchial tree still appears to be normal on bronchoscopic and bronchographic examination. Hence, periodic cytologic study of the sputum as well as repeated roentgen examinations have been suggested for earlier detection (Lerner *et al.* 1961). Cytological examination of pleural fluid is an effective diagnostic technique, and is more sensitive than needle biopsy. Carcinoma cells can be detected in 60 to 70% of patients with pleural metastases.

Intradermal tests: The intracutaneous tuberculin and fungal tests are universally used to detect past and present infection with mycobacteria and fungi. In the southern United States dermal reactivity to antigens prepared from atypical mycobacteria are being studied because it has been learned that the same persons who react weakly to purified protein derivative will react fairly strongly to the new antigens. Some of these persons become ill with a pulmonary disease which simulates pulmonary tuberculosis very closely save for the absence of tubercle bacilli in the sputum or gastric contents. The full import of human infection with atypical mycobacteria is yet to be clarified.

The Kveim test is accepted as a basic technique for the diagnosis of active sarcoidosis. More than three of every four patients with active lesions will give a positive reaction. False positive reactions occur in less than 2% of tests. The test tends to become negative as the sarcoidosis abates (Siltzbach & Ehrlich 1954, James & Thomson 1955, Siltzbach 1961).

Biochemical Abnormalities

Hypercalcæmia, hypercalciuria: Abnormal calcium metabolism is found in sarcoidosis, beryllium disease and occasionally in patients with bronchogenic carcinoma or Hodgkin's disease without apparent osseous involvement. Although increased gastro-intestinal absorption of calcium is present, a satisfactory explanation for this phenomenon has not yet been found.

Hyperglobulinæmia: This abnormality occurs in about one-third of the patients who suffer from sarcoidosis or the Hamman-Rich syndrome and the finding has led to speculation that these two disorders may be expressions of an underlying hypersensitive state.

Hypogammaglobulinæmia: Patients with hypogammaglobulinæmia deal poorly with bacterial infections and are subject to frequent attacks of pneumonia which tend to become chronic. On the other hand, these patients withstand most viral infections.

Elevated lactic dehydrogenase (L.D.): Recently, Wroblewski & Gregory (1961) subjected lactic dehydrogenase (L.D.) to starch gel electrophoresis and thus detected five separate iso-enzymes. They also determined that the level of enzymes designated as L.D. 4 and L.D. 5 was elevated in patients with myocardial infarctions, and the level of enzymes L.D. 2 and L.D. 3 was elevated in patients with pulmonary infarction.

Elevated blood serotonin and 5-HIAA urine levels: The carcinoid syndrome was first described in patients with metastasizing carcinoid tumours of the gastro-intestinal tract. This syndrome has also been seen with metastasizing bronchial adenoma (Warner & Southren 1958). Patients with the carcinoid syndrome display typical attacks of flushing, diarrhœa, bronchoconstriction, œdema and structural abnormalities of the heart. The level of 5-hydroxytryptamine (serotonin) in the blood is usually elevated as is the level of the 5-hydroxyindoleacetic acid in the urine (5-HIAA). Recently two patients with bronchial adenomas exhibited raised levels of both substances with symptoms of the carcinoid syndrome. Surgical removal of the tumours resulted in a prompt fall to normal level of blood serotonin and urinary 5-HIAA levels (R R P Warner 1961, personal communication). The carcinoid syndrome may also occur with oat cell carcinoma.

REFERENCES

Carstensen B (1954) *Nord. med.* **52**, 981
Daniels A C (1949) *Dis. Chest* **16**, 360
Donohoe R F, Katz A & Matthews M J (1957) *Amer. J. Med.* **22**, 883
Hutcheson J B & Waldorf V R (1960) *Amer. Rev. resp. Dis.* **81**, 340
James D G & Thomson A D (1955) *Quart. J. Med.* **24**, 49
Klassen K P, Anlyan A J & Curtis G M (1949) *Arch. Surg.* **59**, 694
Lerner M A, Rosbach H, Frank H A & Fleischner F G (1961) *New Engl. J. Med.* **264**, 480
Löfgren S, Snellman B & Nordenstam H (1955) *Acta chir. scand.* **108**, 405
Mestitz P, Purves M J & Pollard A C (1958) *Lancet* ii, 1349
Rabin C B, Selikoff I J & Kramer R (1952) *Arch. Surg., Chicago* **65**, 822
Siltzbach L E (1961) *Amer. J. Med.* **30**, 495
Siltzbach L E & Ehrlich J C (1954) *Amer. J. Med.* **16**, 790
Warner R R P & Southren L (1958) *Amer. J. Med.* **24**, 903
Weed L A & Andersen H A (1960) *Dis. Chest* **37**, 270
Wroblewski F & Gregory K F (1961) *Ann. N. Y. Acad. Sci.* **94**, Art. 3, p. 912

Dr L S Carstairs (*London*)

The Interpretation of Shadows in a Restricted Area of a Lung Field on the Chest Radiograph

This is an analytical problem. One approach to it can be summarized as follows: An attempt may be made to assess the physical characteristics of the objects responsible for the shadows, in terms of their size, shape, density and orientation to the X-ray beam. These are then related to the known structure of normal and pathological tissues. Finally the shadows are matched to an anatomical or histological entity. In this context any interpretation which derives from experience and clinical judgment must necessarily be disregarded.

Examples of encysted interlobar effusion simulating an intrapulmonary solid lesion, miliary tuberculosis, honeycomb lung, hæmosiderosis, silicosis, infective changes in emphysema, carcinomatous lymphangitis and bronchiectasis were shown to illustrate the difficulties encountered in the interpretation of pulmonary shadows when isolated from the overall chest radiograph. Certain problems emerged, particularly when the quantity of abnormal structures approached or equalled the quantity of normal lung tissue. The radiographic picture of an excised lung may have little similarity to the picture obtained when the lung is enclosed within the thorax. In order to penetrate the walls of the thorax, the quality and quantity of radiation is such that much of the finer lung detail is obliterated. If it were possible in routine clinical work to obtain a true radiographic representation of the lung, then considerable re-education would be required.

Part of the problem in routine chest radiography is to know whether the shadows we see represent single structures or whether they are summation effects produced by the superimposition of many shadows. In the case of large

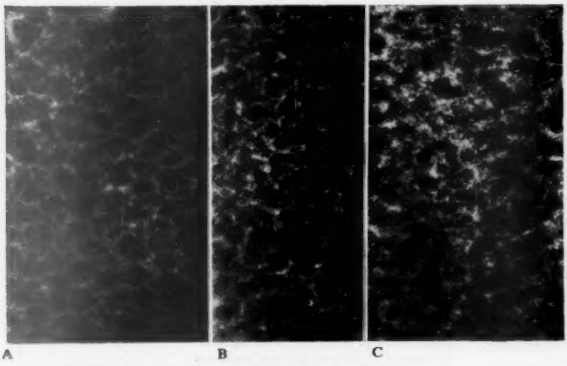


Fig 1 *Plastic foam:* A, *0·5 cm thick.* B, *5·5 cm thick.* C, *18 cm thick*

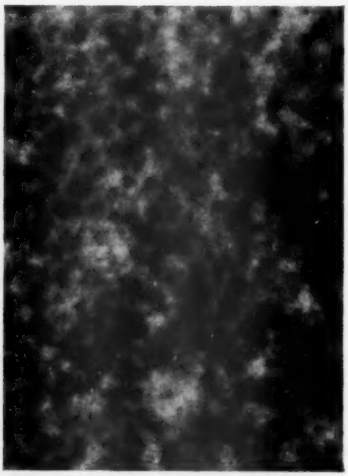


Fig 3 *20-cm-thick layer of discrete nodules, 2–5 mm in width.* × *4*

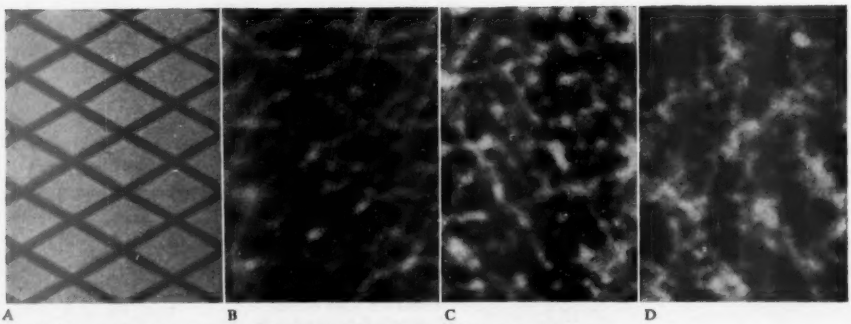
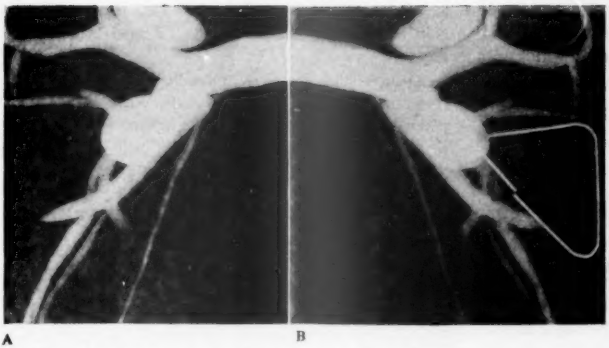


Fig 2 *Linear plastic lattice:* A, *1 layer.* B, *7 layers.* C, *40 layers.* D, *80 layers*



A B

Fig 4 A, *Model lung, wax slabs, 18 cm of plastic foam, plasticine hilum.* B, *more than a hundred of 2 mm 'nodules' have been placed in the triangle*

vessels, calcifications, flat structures seen edge-on, and large shadows surrounded by well aerated lung, there is no difficulty. Their shadows correctly represent their physical state. It is with the finer shadows, when present in large numbers, that difficulties arise.

Experiments to investigate these points have been made. To simulate the background reticular pattern of normal lung, moistened plastic foam was used. In sections varying in depth from 0·5 to 18 cm (Fig 1) the general pattern is retained; but with increasing depth of layer, the components of the pattern appear to increase in thickness. This is a summation effect. The pattern given by a layer width of 18 cm could not have been produced by single structures (precautions were taken to ensure that the lowermost layers were not excessively moist and an air-gap was introduced).

To simulate linear opacities lying at right angles to the X-ray beam, a plastic lattice is used. The effect of superimposing 7, 40 and 80 layers of this lattice is shown in Fig 2. With 80 layers the pattern becomes irregularly nodular in appearance with ill-defined areas of relative translucency.

Fig 3 shows the result of radiographing a 20-cm-thick collection of discrete solid nodules, varying in size from 2–5 mm. Although nodular in appearance, there are numerous well-defined circular shadows giving the appearance of hollow structures.

Finally a model lung was made. It consisted of 18 cm of moistened plastic foam sandwiched between slabs of wax and containing an artificial hilum made of plasticine. The effect of placing approximately 100 nodules 2 mm in diameter in a small portion of this model is shown in Fig 4.

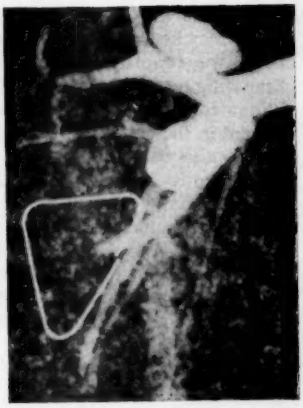


Fig 5 *Model lung. Thousands of 2 mm 'nodules' have been introduced at many levels throughout the model*

Fig 6 *A plasticine 'hilum' placed against the 20-cm-thick layer of 'nodules'. The finer vessels cannot be seen*

Under these ideal conditions a faint alteration in the texture of the area can be seen where the nodules summate with the background pattern.

When the model was loaded with thousands of 2 mm nodules at all depths a 'nodular pattern' was obtained, the individual components of which appeared to be due to summation shadows (Fig 5). The effect of placing another model of the hilar vessels against a background consisting of a 20-cm-thick layer of nodules is seen in Fig 6. The fine vascular shadows disappear and the larger shadows become ill-defined in outline.

From these initial experiments some conclusions can be drawn. In conditions of good contrast, that is when the relative volume of air to

solid structures is high, small opacities of tissue density may be visible if their diameter in the line of the X-ray beam adds materially to the thickness of the solid background (detail of which is largely obliterated in normal radiography). Other factors inherent in the behaviour of X-rays in tissue and air may also be of importance. When the background density has markedly increased, the interpretation of any shadows in terms of individual structures becomes difficult. Nodular structures may look cystic, linear structures may look nodular and an increase in the quantity of background reticulation may give the impression that the components of this network have become thicker.

I should stress that these are academic exercises and that experience and clinical judgment are the prime factors in the interpretation of the chest radiographs in chronic lung disease.

Dr A J Karlish and Dr A L Tárnoky (*Reading*)

Mucoviscidosis and Chronic Lung Disease

Mucoviscidosis, or cystic fibrosis of the pancreas, is being reported with increasing frequency in adults (Di Sant' Agnese & Andersen 1959, Peterson 1959, Koch *et al.* 1960, Bernard *et al.* 1961); in most of these cases respiratory disease is the predominant feature, with little or no pancreatic deficiency. Di Sant' Agnese's discovery (Di Sant' Agnese *et al.* 1953) of electrolyte disturbances resulting in loss of sodium and chloride in the sweat has, by extending the field of diagnosis, gradually modified our view of the disease. It is now realized that pancreatic function may be normal or slightly reduced, but that respiratory involvement is rarely absent. The basic lesion in the bronchi – as in other affected organs – appears to consist of changes in the mucous glands with secretion of an abnormally viscid mucus, giving rise to obstructive bronchiolitis and chronic infection.

Mucoviscidosis is believed to be inherited by a recessive mode of transmission with fully manifest disease in homozygotes and partial forms or no expression in heterozygotes (Childs 1956) – the latter forming, on this hypothesis, a significant proportion of the population (Carter 1952).

Since 1958 we have used the sweat test in a study of chronic nonspecific lung disease and have shown that a significant proportion of adult patients have increased levels of sodium and chloride in their sweat (Karlish & Tárnoky 1960). We now present a report of further investigations, which include 220 subjects: 93 patients with chronic lung disease, classified as bronchitis, asthma or bronchiectasis, 72 controls, either healthy or with various unrelated conditions, and 55 close relatives (parents, children, siblings and parents' siblings). The 93 patients and 60 of the controls were matched for age: of the former, 32 were aged 1–14 (mean 8) and 61 were 15–67 (mean 37); of the controls, 15 were 1–14 (mean 7) and 45 were 15–67 (mean 37) – in addition 12 younger controls were aged 3 months to 3 years (mean 15 months). Sweat tests were carried out by the heat method (Shwachman *et al.* 1955, Tárnoky 1958), and sodium and chloride levels were estimated in all 220 subjects. Bronchograms were obtained in 67 cases.

Results

The distribution of sweat electrolyte levels in 93 patients and 60 controls is shown in Fig 1. Our dividing lines are 65 mEq/l. for chloride and 80 mEq/l. for sodium. The group of abnormally high values at the top right hand corner of Fig 1 comprises 26 patients, of whom 22 are 15–67 years old,

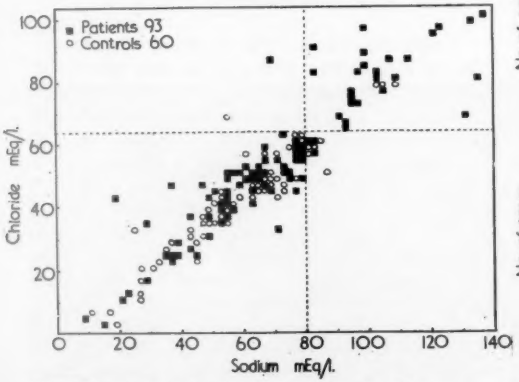


Fig 1 *Sweat electrolyte levels in chronic lung disease*

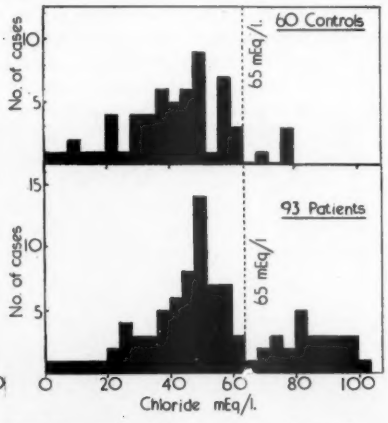


Fig 2 *Sweat chloride in patients and controls*

Table 1
Sweat chlorides in relation to age: 93 patients and 60 controls

Age	*No. of patients*	*No. of patients with raised chloride*	*No. of controls*	*Chlorides*
1–14	32 (mean age 8)	4 69–96 mEq/l. (mean 85)	15 (mean age 7)	3–62 mEq/l. (mean 33)
15–67	61 (mean age 37)	22 65–102 mEq/l. (mean 84)	45 (mean age 37)	12–80 mEq/l. (mean 48)

with chloride values of 65–102 mEq/l. (mean 84) and sodium of 83–137 mEq/l. (mean 105). In contrast, the 60 controls have a mean chloride of 42 mEq/l. and 58 mEq/l. of sodium; only 4 adults have raised chloride values (70–80 mEq/l.). The electrolyte levels in our 'abnormal' group are somewhat lower than those found in children with the fully manifest disease; our upper normal limits (65 mEq/l. chloride) are within ± 10 mEq/l. of results quoted by other authors.

The division and overlap of normal and raised levels of chlorides is better shown in Fig 2. In this, the controls approximate quite well to a normal distribution, while the patients show a bimodal curve consisting of the normals as above and a smaller, reasonably well-differentiated group with abnormal chloride values. One of the factors for this overlap among adults is illustrated in Table 1, which shows sweat electrolytes analysed in relation to age. Among controls mean chloride values are: 48 mEq/l. in adults aged 15–67, 33 mEq/l. among children aged 1–14, and 18 mEq/l. in a still younger group of 12 infants not shown in Table 1. Mean 'abnormal' values (84–85 mEq/l.) among patients are similar in both age groups, making it clear why there is more overlap and less separation in adults than in children. Similar considerations apply to sodium levels. Other factors influencing the salt content of sweat are more fully discussed elsewhere (Tárnoky & Karlish 1961).

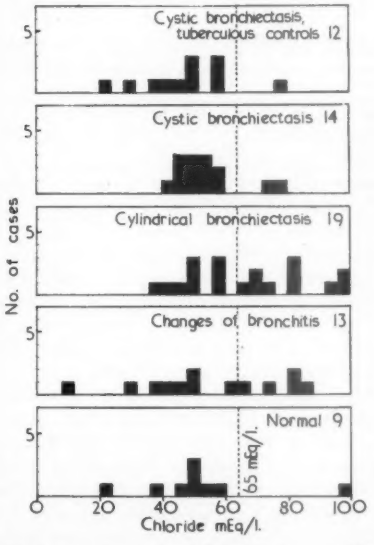


Fig 3 *Bronchographic findings and sweat chloride levels (67 cases)*

Bronchographic studies: Sixty-seven bronchograms were obtained: 55 among the patients with chronic lung disease and 12 among tuberculous controls. Of the 55, 9 are normal, 13 show changes consistent with bronchitis and 33 have various degrees of bronchiectasis. A significant number of patients classified as bronchitis or asthma show structural changes of the bronchial tree, and the lines of division from bronchiectasis are not always easily drawn.

The relationship of bronchographic findings to sweat chloride value is shown in Fig 3. Among 9 patients with normal bronchograms one had high sweat chloride, while of 13 with bronchitic changes 5 had raised values. Of the 33 patients with bronchograms showing evidence of bronchiectasis, 12 had raised chlorides. While many of the 33 bronchograms show dilatations of a mixed cylindrical and cystic character, 19 of the 33 are predominantly cylindrical and 10 of these had abnormal sweat electrolytes; of the 14 with mainly cystic bronchiectasis only 2 had raised values. Of the 12 tuberculous controls with cystic dilatations one had abnormal chloride levels. These findings are consistent with Bodian's report (1952) based on 62 autopsies of children with fibrocystic disease: 'Bronchiectasis was principally of the tubular type; saccular bronchiectasis was only observed in 2 cases'. Peterson (1959) and Koch *et al.* (1960) also noted this correlation with cylindrical bronchiectasis.

Family studies: 55 close relatives belonging to 15 families have so far been tested: (*a*) eight families of fibrocystic children (6 confirmed at autopsy): Of 33 relatives tested, 13 had abnormally high chlorides (65–107 mEq/l., mean 83); 2 of the 13 have chronic bronchitis, 2 have asthma, 1 has

bronchiectasis and 1 duodenal ulcer. A striking example is shown in Fig 4. (*b*) Seven families of patients found to have chronic lung disease and

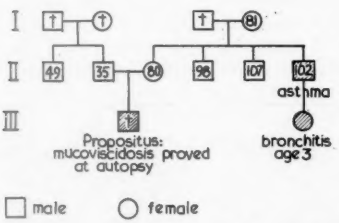


Fig 4 *Family study of case of meconium ileus with sweat chloride values. The index case was a 5-day-old baby whose mother and her three brothers had abnormal sweat chlorides (80–107 mEq/l.). One of the three brothers has asthma and his small daughter has already had two hospital admissions for bronchitis. The grandmother (on the 'abnormal' side) also has raised chlorides. The baby's father and uncle are normal*

high sweat electrolytes: Of 22 relatives examined 8 had raised chlorides (65–107 mEq/l., mean 80); 3 of the 8 have chronic bronchitis, 1 has asthma, 1 gastric ulcer, and 1 diabetes. In one such family the index case, aged 48, has bronchiectasis and a chloride level of 84 mEq/l. His 2 brothers and 2 young nieces all have raised chloride levels (65–107 mEq/l.). One of the 2 brothers is a diabetic and the 2 grandparents had severe bronchitis.

These results suggest a genetic relationship between fully manifest mucoviscidosis and cases of chronic lung disease with raised sweat electrolytes.

Association with peptic ulcer: There were 9 cases of peptic ulcer (6 duodenal, 1 gastric, 2 unspecified) among the 35 males 15–67 years old in this series; 4 had abnormally high sweat chlorides (69–96 mEq/l.). This incidence agrees with reports of clinical and autopsy studies, showing 15–27% of peptic ulcer in cases of pulmonary emphysema (Silen *et al.* 1959).

Conclusions: The hypothesis that some cases of chronic lung disease in adults may be partial forms of mucoviscidosis has gained support in the last two years.

The evidence we have presented is based on results of sweat tests, family studies and bronchographic correlation. The significance of sweat tests in adults has been recently contested by Anderson & Freeman (1960) who, using intradermal mecholyl stimulation, suggest that the raised sweat values reported are within the range of normal variation.

As we have pointed out (Table 1), sweat electrolyte levels rise through childhood and are distinctly higher after puberty, but allowing for this our data still show that among adults with chronic lung disease there is a significantly higher proportion of individuals with abnormal values compared with controls matched for age.

Acknowledgments: We are greatly indebted to Dr W S Holden, Radiologist, United Oxford Hospitals, for his important part in the interpretation of the bronchograms, and to the late Dr J J Kempton, Pædiatrician, Royal Berkshire Hospital, for help with the family studies.

REFERENCES

Anderson C M & Freeman M (1960) *Arch. Dis. Childh.* **35**, 581
Bernard E, Israel L & Debris M-M
(1961) *J. franç. Méd. Chir. thor.* **15**, 447
Bodian M ed.
(1952) Fibrocystic Disease of the Pancreas. London; p 121
Carter C O (1952) In: Fibrocystic Disease of the Pancreas. Ed. M Bodian. London; p 50
Childs B (1956) In: Fibrocystic Disease of the Pancreas. 18th Ross Pediatric Research Conference. Ross Laboratories, Columbus, Ohio; p 87
di Sant' Agnese P A & Andersen D E
(1959) *Ann. intern. Med.* **50**, 1321
di Sant' Agnese P A, Darling R C, Perera G A & Shea E
(1953) *Pediatrics, Springfield* **12**, 549
Karlish A J & Tárnoky A L (1960) *Lancet* ii, 514
Koch E, Bohn H, Rick W & Hartung W
(1960) *Internist, Berlin* **2**, 35
Peterson E M (1959) *J. Amer. med. Ass.* **171**, 1
Shwachman H, Leubner H & Catzel P (1955) *Advanc. Pediat.* **7**, 249
Silen W, Eiseman B & Brown W
(1959) *Amer. Rev. resp. Dis.* **80**, 155
Tárnoky A L (1958) Clinical Biochemical Methods. London
Tárnoky A L & Karlish A J
(1961) *Proc. Ass. clin. Biochem.* **1**, 124

Section of Comparative Medicine

President J M Alston FRCPEd

Meeting March 15 1961

Hormonal Control of Fertility in Man and Animals

Professor A S Parkes (*London*)

The Biology of the Reproductive Hormones

The anterior pituitary body is usually regarded as the focal point of the endocrine system because it produces the trophic hormones which activate the ovary and thyroid, adrenal and mammary glands and is in turn regulated by humoral or neurohumoral feed-back mechanisms from these glands and the female reproductive tract. This system, as far as it relates to the reproductive organs and adrenal cortex, is shown in Fig 1, which is self-explanatory subject to the following notes:

(1) The effect of the ovary on the adrenal is seen only where there is sex dimorphism or cyclic changes in the adrenal. In the same way, the production of gonadal-like hormones by the adrenal with consequent effects on the accessory reproductive organs becomes manifest only under abnormal circumstances. The important systemic effects of the adrenal-cortical hormones need not be considered here.

(2) Events in the female reproductive tract influence the ovary by reflex stimulation of the hypothalamus and thence of the adenohypophysis. Thus, mating is necessary for the induction of ovulation in the rabbit and the ferret, and in the rat and mouse for the stimulation of the corpus luteum of ovulation required to interrupt the five-day œstrous cycle and permit implantation of the fertilized egg (sterile mating is followed by a pseudopregnancy which lasts twice as long as the usual di-œstrous interval in the unmated female). In other species implantation of the fertilized egg, or possibly even the presence of a fertilized egg in the reproductive tract, results in maintenance of the corpus luteum which would otherwise undergo regression. In some species tight timing is implied. Thus, in man, the fertilized egg becomes implanted only a very few days before the corpus luteum would otherwise begin to hypotrophy preparatory to the next menstrual period.

(3) The presence of high levels of œstrogen or progesterone in the body reduces the secretion of FSH and LH, presumably through the mediation of the hypothalamus, so that overstimulation of the ovary is prevented. In the same way production of milk by the mammary gland in excess of demand causes reflex inhibition of prolactin secretion, whereas a strong suckling stimulus applied to the nipple stimulates the secretion of prolactin.

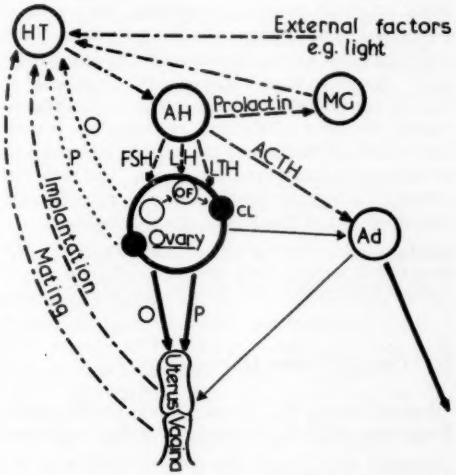


Fig 1 *Endocrine and neurohumoral interactions concerned in reproduction*
Ad, *adrenal cortex*. AH, *adenohypophysis*. HT, *hypothalamus*. MG, *mammary gland*. OF, *ovarian follicle*. CL, *corpus luteum*. FSH, *follicle stimulating hormone*. LH, *luteinizing hormone*. LTH, *luteotrophin* (*prolactin*). O, *Œstrogen*. P, *progesterone*.
———— *Major effects of steroid hormones.*
———— *Minor effects of steroid hormones.*
— — — — — *Major effects of hypophysial trophic hormones.*
— · — · — · — *Neurohumoral effects concerned in regulating the adenohypophysis through the hypothalamus.*
. . . . . *Ovarian hormone feed-back mechanism to the adenohypophysis*

(4) The hypothalamus and thence the adenohypophysis and the reproductive organs are affected by exteroceptive factors such as light, so that the anœstrous ferret, for instance, can be brought into œstrus during the winter by exposure to artificial light during the evenings.

This outline of the endocrine effects concerned in regulating the reproductive cycle shows a complex and delicately-balanced system and the surprising thing is not that there is sometimes a breakdown but that breakdowns are not more frequent.

A remarkable extension of our knowledge of exteroceptive factors influencing the reproductive processes arises from the work of Bruce (1959), who has shown that pregnancy is blocked in a large proportion of newly-mated female mice exposed to the smell of males of a different strain. The immediate cause of the block is failure of implantation, which can be corrected by the administration of exogenous prolactin and presumably depends therefore on olfactory inhibition of luteotrophin secretion and consequent corpus luteum failure. The nature and source of the odour producing this effect is unknown, but it evidently belongs to the group of substances now attracting much attention, namely, substances which are not concerned as hormones with the integration of the individual but are concerned with the integration of a population of individuals. Karlson & Butenandt (1959) have coined the name 'pheromones' for these substances, which include the sex attractants of moths and the recently isolated and synthesized queen-bee substance, and we are evidently seeing the birth not of a branch of endocrinology but of the science of exocrinology.

REFERENCES
Bruce H M (1959) *Nature, Lond.* **184,** 105
Karlson P & Butenandt A (1959) *Ann. Rev. Entomol.* **4,** 39

Dr Margaret Hadley Jackson (*Exeter*)

Observations on the Use of Certain Orally Active Progestogens for the Control of Fertility in Women

The story of the detection and isolation of the steroid hormones, and of their synthesis and modification by ingenious chemical and physiochemical techniques is an excellent example of the extreme value of close collaboration between scientists and commercial firms. Fundamentally it was the insight of such scientists as Zondek and Laqueur that initiated collaboration of this sort. It is difficult to visualize the immense amount of work, ingenuity and money that goes into the marketing of a new product. Dozens, and in some cases hundreds, of possible compounds are synthesized and discarded for one that may be useful. The orally active progestogens originated from this kind of laborious and at times unrewarding work. Every new compound has to be screened for its range of therapeutic effectiveness, its toxicity and general acceptability. These synthesized steroids, no less than the natural hormones, possess a wide range of biological activities some of which are not only unnecessary but may even be undesirable in a particular therapeutic application. There is therefore a need for what Hartley (1957) has so neatly called 'tailored steroids'. There have already been considerable advances in that direction; the observation, for example, that removal of the methyl group at position 19, or the addition of one at position 6, makes for greater progestogenic activity opened up wide therapeutic fields. Although these progestogens started life as agents for aiding fertility by their action on the endometrium they are now being successfully used to limit fertility by inhibiting ovulation. This property is shared by other steroids, notably the androgens and œstrogens, but both these hormones produce other effects which are undesirable in the control of fertility.

Besides the above-mentioned progestational effect on the endometrium and the inhibition of ovulation, the progestogens have a number of actions which are exhibited in varying degrees by the different compounds. They have anabolic and fluid retaining properties; some androgenic, myotrophic and thermogenic activity; mild corticoid and œstrogenic activity; gonadotrophin inhibitory and anti-œstrogenic effects; influence on water and electrolyte excretion and on mating behaviour. All these activities must be assessed first by laboratory screening tests and later by careful clinical trials before a compound is offered for clinical use.

Previous Clinical Trials

Much of the early clinical work with oral progestogens was planned and carried out in the United States of America by Pincus and Rock, at first with a view to enhancing fertility but later as a contraceptive measure (Pincus 1958; Pincus, Rock & Garcia 1958, 1959; Pincus, Rock, Chang & Garcia 1959; Rock *et al.* 1956; Rock *et al.* 1957, 1959). Of a large number of progestational compounds tried, the most promising were norethynodrel[1] and norethisterone.[2] Extensive trials

[1]Norethynodrel = 17α-ethinyl-17-hydroxy-5(10)-œstren-3-one. This is available in Britain as Enavid (Searle) in 5 mg and 10 mg tablets containing 0·075 mg and 1·5 mg ethinylœstradiol 3-methyl ether, respectively. The 5 mg tablet is also marketed specifically for oral contraception as Conovid. Enovid (Searle) is the name of the American preparation.

[2]Norethisterone = 17α-ethinyl-17-hydroxy-19-Nor-4-androsten-3-one = 17-ethinyl-19-nortestosterone. This is available in Britain as Primolut N (Schering A.G.) and in the United States as Norlutin (Parke Davis).

have been made of both these compounds. The results of those in Puerto Rico and Haiti, which were started in 1956 by Pincus (*see* Garcia *et al.* 1958), and in Los Angeles by Tyler (Tyler 1959, Tyler & Olson 1959) are well known. From these trials and others in Mexico a considerable mass of clinical evidence is accumulating on the other side of the Atlantic.

Trials are also running in Europe, Australia and Japan but the number of patients treated is small and little has been published. A trial carried out in Belgium with norethisterone acetate[1] was described by Peeters *et al.* (1960). The ovulation inhibitory action of the Italian preparation Farlutal[2] has been described (Goisis & Cavalli 1959) but its trial as a contraceptive agent has not been reported. In this country small, carefully controlled, trials of norethynodrel, norethisterone and norethisterone acetate have been in progress for nearly two years; larger clinical trials have recently been set up in Birmingham and Slough, both with norethynodrel. Another is to be started shortly under the auspices of the Council for the Investigation of Fertility Control and run from the Family Planning Association headquarters using norethisterone with added œstrogen. Two orally active progestogens produced by British Drug Houses have had preliminary clinical screening and are almost ready for trial as oral contraceptives. These are not 'nor' preparations but have an added methyl group at 6; one is similar to Farlutal (Farmitalia) and Provera (Upjohn).

Among other available progestogens, norethandrolone (17-ethyl-19 nortestosterone, Nilevar, Searle) was rejected as an oral contraceptive because of its marked anabolic effect; methylœstrenolone (Orgastrone, Organon) for its androgenic effects; allylœstrenol (Gestanin, Organon) and dimethisterone (Secrosteron, B.D.H.) because they had little ovulation inhibitory activity.

A good deal is already known about the short-term effects of these progestogens in women, and a little about their effect in men (Heller *et al.* 1958, Nelson 1959), but it will be many years before a complete answer can be given as to their possible long-term effects. There is so far no evidence that prolonged administration of progestogens is harmful and in particular there is no evidence that they are carcinogenic. Œstrogens, on the other hand, are known to be potential carcinogens, but these are used in only very small amounts in oral contraceptives and although administration is prolonged, it is not continuous; there is a break in the tablet-taking at regular intervals so that there may be a withdrawal bleeding. Most investigators in charge of clinical trials have concluded that it is desirable to incorporate a very small dose of œstrogen with the progestogen in order to maintain the integrity of the endometrium, to prevent 'spotting' (break-through bleeding) and to keep the cycles regular; but since there is some conflicting evidence on this point, the use of a progestogen alone cannot be excluded.

[1]Norethisterone acetate = 17β-acetoxy-17α-ethinyl-œstr-4-en-3-one. This is not generally available in this country but is being used in clinical trial as S.H. 639 (Schering A.G.). It is available in the United States as Norlutin A (Parke Davis).

[2]6α-methyl-17α-hydroxyprogesterone acetate.

Personal Observations

These are based on clinical trials of norethynodrel, norethisterone and norethisterone acetate. Women, all multiparous, many of them problem patients with big families, some with severe menorrhagia, have been allocated at random to two main groups, one to receive norethynodrel, the other equally divided into the recipients of two norethisterone preparations. The first tablets were distributed in March 1959 and the groups have been built up gradually since then so as to contain between 25 and 30 patients in each and are now being kept at that figure by adding fresh entrants as and when previous participants fall out. Out of 32 entrants to the first group there are 25 current cases and in the second there are now 12 in each sub-group out of 16 and 15 entrants respectively.

Dosage of Norethynodrel

5 mg tablets (containing 0·075 mg œstrogen)
2·5 mg tablets (containing 0·15 mg œstrogen)
2·5 mg tablets (containing 0·10 mg œstrogen)

The œstrogen used in the norethynodrel tablets which have been supplied by Searle, is ethinyl-œstradiol-3-methyl-ether. Of those that were started on the 5 mg tablets the majority have had their dosage cut to 2·5 mg. A few that started on 2·5 mg have later been given 5 mg tablets. The adjustment of the dose (in particular in the amount of œstrogen) to avoid minor troubles such as breast discomfort and 'spotting' is a highly individual affair and needs a little dexterity on the part of the doctor. I am hoping that the use of the vaginal smear technique will make the choice of the correct dose and drug easier to arrive at.

Dosage of Norethisterone

Norethisterone 5 mg
Norethisterone 2·5 mg
Norethisterone acetate 4 mg
Norethisterone acetate 2 mg

All preparations of norethisterone and its acetates have been supplied by Schering and contain no added œstrogen. All subjects receiving norethisterone have been started on 5 mg and only a few

have been reduced to 2·5 mg. The acetate has been given in 2 mg strength in about half the cases from the start.

Instructions and Records
Each patient is given written instructions and a card on which to record bleeding and 'spotting', intercourse and the taking of tablets. Weight and blood pressure readings are recorded at intervals and notes are kept of symptoms and general comments.

Side-effects and Results
Side-effects have not been troublesome in either group and no one, up to the time of writing, has withdrawn from the trial because of them. In all cases the dose has been adjusted (usually in a downward direction) if the patient has suffered any side-effects. Gastrointestinal symptoms and breast discomfort are commoner with norethynodrel; whereas a bloated feeling, slight weight gain and hunger, headaches and irregularities of cycles (including breakthrough at short intervals and no bleeding at the end of the twenty days on tablets) are more often met in patients on norethisterone and norethisterone acetate. I have no doubt that this rather troublesome irregularity could be largely avoided by adding œstrogen but I have purposely avoided doing this in order to learn how well patients would tolerate this degree of irregularity and whether with persistence a more regular rhythm would become established. Provided a woman can be persuaded that she need not worry if a bleeding does not appear she will usually become adjusted to irregularity and in the majority of cases the cycles do tend to get more regular with time. Libido has shown little change and most of the patients feel well while taking the tablets; the few who have felt vaguely unwell have been taking one of the norethisterone preparations. No one has conceived while taking the tablets correctly; three took their tablets wrongly and conceived forthwith (2 in the Searle and 1 in the Schering group). Three have withdrawn, one because she no longer needed birth control, one because she was frightened by what she had read in the papers and one because she had a serious motor accident. There have been no instances of masculinization, gross œdema or consistent rise in blood pressure.

Basal temperature charts have been kept by the majority of patients and they tend to be quite erratic, particularly in the norethynodrel group. With the norethisterone preparations a rise within twenty-four hours of the first tablet is not infrequently seen.

Post-coital examination of cervical mucus is carried out whenever possible; about 40 such examinations have been made. In the norethynodrel group nearly 50% show motile sperm and the mucus tends to be moderately plentiful and quite elastic at any point in the cycle; whereas in the norethisterone group (on pure progestogens) the mucus is scanty and tenacious, and if sperm are present, they are invariably immotile.

Vaginal smears, stained with a modification of the Papanicolaou technique, are being studied. The work is not yet far enough advanced to be worth reporting.

Endometrium for biopsy is collected from all patients at various points in the cycle. The tendency is towards atrophy which may develop rapidly or quite slowly; in some a mixed picture is produced; the fibrillar type of stroma is seen more commonly in patients on the norethisterone preparations than in those on norethynodrel. It was noted that in the latter group of patients the endometrium can become just as atrophic as in those on norethisterone in spite of the added œstrogen; indeed, the woman (aged 32 and para-5) with the most marked and persistent degree of atrophy has been on norethynodrel tablets which contain œstrogen. Before starting to take the tablets she was menorrhagic with a hyperplastic endometrium. The character of the changes in the histological picture is somewhat different in the two groups:

In the *norethynodrel* cases up to cycle day nineteen (i.e. after fifteen days on tablets) subnuclear vacuolation may be found in a few glands and it appears very soon after the first 2 or 3 tablets have been taken (i.e. by the seventh or eighth day of the cycle). It seems to be most marked on cycle days sixteen and seventeen (i.e. after twelve or thirteen days on tablets). Towards the end of the twenty days on tablets the glands tend to become small and atrophic, the cells having lost height and substance and their nuclei being pyknotic. The stroma may be loose and œdematous or dense and cellular showing the characteristic fibrillar change; towards the end of the cycle there may be patches of quite marked decidual response but where the endometrium becomes really atrophic, none of these changes can be seen.

In the cases on *norethisterones* (which contain no added œstrogen) subnuclear vacuolation does not appear at any point in the cycle and the glands remain small and uncoiled but the nuclei do tend to line up near the basement endometrium. The stroma in these cases is mostly densely cellular from an early stage with the characteristic fibrillar appearance; it may show decidual change later but the individual cells and nuclei are

smaller and stain more darkly than in normal late secretory endometrium or in the norethynodrel cases.

The British Drug Houses experimental tablets, 1298 and 1921, have so far only been subjected to clinical screening. Three tests have been used: (*a*) Postponement of menstruation (with and without œstrogen) as suggested by Greenblatt *et al.* (1958) and Swyer *et al.* (1960); this cannot be achieved with either drug with doses up to 20 mg daily unless the progestogen is combined with a small dose of œstrogen. (*b*) The building of secretory endometrium after œstrogen priming in a previously atrophic endometrium. A good secretory endometrium can be built in one previously atrophic after initial priming with œstrogen in response to both products in doses of 10 and 5 mg daily, given from cycle day sixteen or seventeen. (*c*) Inhibition of ovulation, with and without œstrogen. There is some evidence that both drugs will inhibit ovulation in doses of 10 and 5 mg daily, provided the tablets are given from cycle day five, say, onwards. Both have a marked thermogenic effect, the rise occurring within twenty-four hours of the first dose. Side-effects have been variable, some patients complaining of little or nothing; others felt tired and listless and a few felt bloated with premenstrual tension and headache. There has been no indication of any androgenic effect.

REFERENCES

Garcia C R, Pincus G & Rock J
(1958) *Amer. J. Obstet. Gynec.* **75**, 82, 1333
Goisis M & Cavalli P
(1959) *Minerva ginec.* **11**, 431
Greenblatt R B, Jungck E C & Barfield W E
(1958) *Ann. N.Y. Acad. Sci.* **71**, 717
Hartley F (1957) *J. Pharm., Lond.* **9**, 705
Heller C G, Laidlaw W M, Harvey H T & Nelson W O
(1958) *Ann. N.Y. Acad. Sci.* **71**, 649
Nelson W O (1959) *Proc. VI int. Conf. Planned Parenthood*, New Delhi. London; p 143
Peeters F, Roy M van & Oeyen H
(1960) *Geburtsh. u. Frauenheilk.* **20**, 1306.
Pincus G (1958) *Stud. Fertility* **10**, 3
Pincus G, Rock J, Chang M C & Garcia C R
(1959) *Proc. Planned Parenthood Fed. Amer.* **18**, 1051
Pincus G, Rock J & Garcia C R
(1958) *Ann. N.Y. Acad. Sci.* **71**, 677
(1959) *Proc. VI int. Conf. Planned Parenthood*, New Delhi. London; p 216
Rock J, Garcia C R & Pincus G
(1959) *Proc. VI int. Conf. Planned Parenthood*, New Delhi. London; p 212
Rock J, Garcia C R & Pincus G
(1957) *Recent Progr. Hormone Res.* **13**, 323
Rock J, Pincus G & Garcia C R
(1956) *Science* **124**, 891
Swyer G I M, Sebok L & Barns D F
(1960) *Proc. R. Soc. Med.* **53**, 435
Tyler E T (1959) *Proc. VI int. Conf. Planned Parenthood*, New Delhi. London; p 237
Tyler E T & Olson H J (1959) *J. Amer. med. Ass.* **169**, 1843

Dr G E Lamming (*Nottingham*)

The Use of Hormones to Control the Fertility of Farm Animals

In contrast with experiments in the human, experiments on the use of hormones to control fertility in farm animals are almost invariably concerned with efforts to increase fertility. Only a brief summary can be given here of the more recent contributions in this field, including some from our own laboratory.

The control of reproductive activity in intensively managed farm stock is a delicately balanced self-compensating mechanism which may get out of phase. Reproductive activity does not always respond to exogenous preparations as we anticipate, and there may be wide variations in response between animals and between experiments. We know too little about the endocrine control of reproduction in farm animals to achieve quick results from *ad hoc* field trials. Ample evidence is also available from many experiments that species differences in response to standard hormone preparations preclude the application of the results from experiments in one species to other classes of animals.

The various purposes for which hormones are used to control reproduction are discussed under the following headings: (1) Control of the œstrous cycle during the normal breeding season. (2) Increase of the ovulation rate by the use of gonadotrophins. (3) Overcoming seasonal anœstrus. (4) Reducing the incidence of embryonic mortality. (5) Control of uterine infections.

Control of the Œstrous Cycle During the Normal Breeding Season

Anœstrus is particularly common in cattle and pigs when they are managed intensively, or where nutritional deficiencies (of both macro- and micronutrients) create a metabolic disturbance. In the three major classes of farm stock heavy lactation militates against reproductive activity especially where the young are suckled. Steroid sex hormones, particularly the synthetic œstrogen, diethyl stilbœstrol, will induce œstrus but this is not usually accompanied by ovulation. One successful form of treatment in cows, when the anœstrus is caused solely by a persistent corpus luteum, is its manual removal from the ovary *per rectum;* a fertile heat usually occurs two to four days after such treatment provided the condition is not accompanied by pyometritis. In cases of spontaneous anœstrus the injection of pregnant mare's serum (P.M.S.) gonadotrophin to stimulate development of the ovaries has proved of limited value for there is a wide variation in response. The ovarian follicular response to P.M.S. is

improved if there is a corpus luteum in the ovary and although ovulation may occur if luteinizing hormone is injected it is not accompanied by behavioural œstrus and fertilization does not result even following artificial insemination (Rowson 1951).

In anœstrous cattle, rectal palpation has been shown to stimulate spontaneous activity of the reproductive tract. It has also been suggested that irrigation of the bovine uterus may cause the release of gonadotrophic hormones (Hancock 1948, Smythe 1943), and rectal palpation of the cervix or uterus results in the release of oxytocin as shown by uterine contractions and milk ejection (Hays & VanDemark 1953). Electrical stimulation may be a more practical way of stimulating resumption of activity. Hays & Carlevaro (1959) have stimulated the area of the ovaries, uterus and cervix of cows using 10–15 volts for two seconds. They observed the animals for œstrous behaviour for seven days following treatment. There was no effect in cows treated within fifty days *post partum* but beyond fifty days and in anœstrous cows, œstrus was produced in approximately 50% of animals treated; it occurred spontaneously in only 5% of untreated controls. The authors suggested that the stimulation resulted in the release of oxytocin which then affected the release of gonadotrophins from the anterior pituitary gland. Armstrong & Hansel (1958) also postulated that in the cow oxytocin is associated with the release of gonadotrophin, for normal cows given oxytocin daily from the day of œstrus for eight days came into œstrus one to four days after treatment ceased. When daily injections were begun on the fifteenth day the heifers came into œstrus at the normal time. When these injections were continued to seven days post-œstrus, the animals again came into œstrus soon after treatment ceased. All animals ovulated normally after the induced œstrus. The effects of these treatments require further study.

The availability of forms of progesterone which are active orally has resulted in a new approach to the synchronization of œstrous cycles of animals which are breeding normally. The injection of progesterone intramuscularly has been used by Rowson and his colleagues (Hunter 1953, Hunter *et al.* 1955) to synchronize œstrus in donor and receptor sheep used for egg transplantation, but such a method is too complicated for large-scale practical application. The orally-active form 6α-methyl-17α-hydroxy progesterone acetate (Provera, Upjohn) has been used experimentally to synchronize œstrus in beef cattle. From the limited results available so far, it will synchronize the cycle, œstrus occurring approximately three to four days after dosing ceases (Hansel 1961, personal communication). It is not yet known whether normal levels of fertility may be expected following such treatment. If this method proves successful it could have wide practical application, especially in countries with large beef herds, where many thousands of cattle could be inseminated from valuable bulls by a limited number of technicians. At the present time artificial insemination under such conditions is not practised because of the technical difficulties involved.

Increase of the Ovulation Rate by the Use of Gonadotrophins

The availability of an inexpensive form of gonadotrophin in the form of pregnant mare's serum (P.M.S.) resulted in an interest in experiments to increase ovulation rate particularly in sheep and beef cattle, in order to obtain a high proportion of twins.

In sheep, the injection of a single dose of P.M.S. during the follicular phase of the œstrous cycle can increase ovulation rate, the actual number of eggs shed being influenced by dose rate. Gordon (1958) has completed extensive field trials with sheep using methods developed by Robinson (1951*a*, *b*). His experiments showed that treatment resulted in a significant increase in fertility, the extent depending on the level of dose given, and the greatest increase occurred in flocks of low fertility. There was no evidence that the treatment affected the ability of the ewe to conceive. High dose rates (1,000 i.u.) were not advocated because of the number of quadruplets and quintuplets born which had a higher incidence of neonatal mortality. Gordon (1961, personal communication) has extended his work to further study on the use of P.M.S. in beef cattle and the results of his trials in the Welsh Border district are now becoming available. The cows were injected about the sixteenth or seventeenth day of the twenty-one-day œstrous cycle. Of 356 cows treated 37·4% responded with multiple ovulation. One major problem was that treatment increased the incidence of 'silent heat' (ovulation without behavioural œstrus). Of the treated cattle 14·8% had 'silent heats' and this occurred more frequently where cattle were injected late in the cycle. Of those which were inseminated conception rate appeared normal but there was a higher incidence of embryonic loss in treated cattle which ovulated two or more eggs, especially when ovulation was unilateral.

Before further commercial application in cattle is warranted there is need for study on the factors affecting the response to P.M.S. and why embryonic mortality is higher after multiple ovulation in

cattle but not abnormally so in sheep treated with low doses of P.M.S. In sheep, treatment with P.M.S. is more successful, but the technique should be used only after taking full advantage of good management to increase the ovulation rate.

Overcoming Seasonal Anœstrus

While some breeds of sheep are polyœstrous the majority of breeds in Britain show a period of quiescence or seasonal anœstrus during summer. This may be preceded in breeding ewes by lactation anœstrus so that under normal conditions animals breed only once per year, a factor which limits the utility of sheep in intensive systems. Seasonal anœstrus is characterized by suppressed cycles of follicular development with occasional ovulation, and the occurrence of an annual rhythm of reproductive activity is under photoperiodic control. Experimental control of the diurnal light/dark ratio has been successfully used experimentally to bring sheep into œstrus (Sykes & Cole 1944, Yeates 1949, Hart 1950, and others), but the method is not practicable under farm conditions. Theories have been put forward to explain that in seasonal anœstrus there is probably a failure of the release of luteinizing hormone (L.H.) from the anterior pituitary gland (Kammlade *et al.* 1952, Hutchinson & Robertson 1960) and this theory is compatible with observations of the hypothalamic control of anterior pituitary function (Harris 1955, Clegg *et al.* 1958). There is no clear explanation of the mechanism by which lactation suppresses œstrus in the ewe. The purpose of experiments described here is to use hormones to control the sexual activity of sheep during anœstrus. The response to alteration of the diurnal light/dark ratio is slow but uniform. The use of gonad stimulating preparations (anterior pituitary preparations, human chorionic gonadotrophin, and P.M.S.) usually induces ovulation without heat. If a second injection of P.M.S. is given sixteen to seventeen days after the first injection œstrus may occur, but the degree of response is not uniform and the incidence of behavioural œstrus is low. Recent work has shown that progesterone and œstrogen act synergistically on the nervous system particularly in the production of psychic œstrus (Moore & Robinson 1957). Therefore to induce a higher incidence of behavioural œstrus in sheep accompanied by ovulation, attention has now been turned to the subcutaneous injection of P.M.S. preceded by a series of progesterone injections given intramuscularly.

Dutt (1952, 1953) and Robinson (1954) were successful in obtaining œstrus, ovulation and fertility in non-lactating sheep using spaced intramuscular injections of progesterone followed by subcutaneous P.M.S. More extensive field trials were carried out in England by Gordon (1957, 1958). The percentage of ewes responding varied from 32% to 90% in different flocks using various progesterone pre-treatments. The results of our own experiments in maiden sheep are largely similar (Table 1). Even though œstrus can be induced in a proportion of lactating ewes, the conception rate of those which mate is low. There is no conclusive explanation for this; Gordon (1958) presumed that loss at implantation is responsible rather than failure of fertilization. This led us to compare the efficacy of changes in the light/dark ratio with hormone treatment.

Table 1

The production of lambs from maiden ewes during the non-breeding season
(Allen & Lamming 1959)

Year	*Treatment*	*No. of ewes treated*	*No. of ewes which mated*	*No. of ewes which lambed*	*No. of lambs produced*
1957	6×12·5 mg progesterone +750 i.u. P.M.S.	30	8	5	7
1958	3×50 mg progesterone +850 i.u. P.M.S.	30	18	17	24
1959	3×50 mg progesterone +850 i.u. P.M.S.	26	24	22	24

In a group of 20 lactating ewes injections of progesterone and P.M.S. induced ovulation in 19 ewes and œstrus accompanied ovulation in 12 ewes. There was a complete failure of fertilization which could not be attributed to poor semen quality. Manipulation of the light/dark ratio induced ovulation in all 10 treated ewes and œstrus was observed in 9. Of the ova recovered from these sheep 41% were cleaving normally. Œstrus was preceded by a 'silent heat'.

During treatment of ewes with progesterone and P.M.S., Raeside & Lamond (1956) found that the changes in the histology of the uterus occurring during progesterone pre-treatment were typical of the luteal phase of a normal œstrous cycle, but that the fallopian tubes which are quiescent during anœstrus did not develop their normal structure. We have completed chemical analysis of uterine secretions of maiden and lactating ewes treated with progesterone and P.M.S. approximately four to six weeks *post partum* (Heap 1960). Our results show that the chemical composition of the secretion is changed by hormone treatment and the development of cyclic activity appears important (Heap & Lamming 1961, in preparation). It would appear that the occurrence of a 'silent heat' at the beginning of

Table 2
The production of lambs from lactating ewes during the non-breeding season

Flock No.	*Date*	*Treatment*	*No. of ewes*	*No. mated*	*No. pregnant*	*No. of lambs*	*Comments*
1	16.3.60	*Single* series● 3 × 50 mg progesterone +850 i.u. P.M.S.	21	16	4	7	12 ewes returned naturally in œstrus 16 days later; 8 lambed giving 10 lambs
		Double series■ 3 × 50 mg progesterone +850 i.u. P.M.S. followed by 3 × 50 mg progesterone +850 i.u. P.M.S.	15	14	9	10	Total 27 lambs
2	28.5.60	*Single* series 3 × 50 mg progesterone +850 i.u. P.M.S.	30	28	26	36	2 died during pregnancy Total 36 lambs
3	22.4.60	*Single* as Flock 1	40	20	6	9	One additional ewe in each group aborted twin lambs Total 23 lambs
		Double as Flock 1	40	29	10	14	
4	22.4.60	*Single* as Flock 1	30	10	0	0	7 ewes lambed 16 days later producing 9 lambs
		Double as Flock 1	31	14	3	4	1 ewe lambed 16 days later producing 1 lamb Total 14 lambs

● Progesterone on Day 1, 4, 7. P.M.S. on Day 9.
■ Progesterone on Day 1, 4, 7, 17, 20, 23. P.M.S. on Day 9 and 25.
Flocks 1 and 2 lambs weaned one to two weeks before treatment. Flocks 3 and 4 treated before weaning.

the breeding season has a physiological significance for the level of fertility improves to a maximum at about the third cycle (Dutt 1954), apparently as the result of a higher ovulation rate and a higher rate of fertilization with less abnormal ova and less embryonic mortality. The failure of fertilization in lactating ewes in our experiments does not appear to be due to the form of treatment *per se* since maiden ewes similarly treated in the same period conceived normally. Nor was it related to lactation *per se* for ewes strongly lactating after producing lambs in the autumn have normal conception rates seven to eight weeks *post partum*. Here again a 'silent heat' precedes such breeding activity.

In 1960 it was decided to compare the effect of two series of progesterone–P.M.S. injections with the standard treatment. The results are given in Table 2. The double series of injections increased the incidence of œstrus, and increased the level of fertility but still did not result in normal numbers of lambs born. Better results were obtained in ewes from which the lambs were removed before treatment (Flocks 1 and 2). Where a limited number of additional lactating ewes have been examined under surgical anæsthesia following the second series of injections they have produced fertile ova two days *post coitum*. Further studies are in progress to determine whether the loss occurs before or after implantation.

In summary, hormone treatment can be used successfully to produce extra crops of lambs from maiden sheep during the non-breeding season at a reasonable cost. The optimum time for treatment appears to be as soon as possible after the close of the breeding season. Before the problem of breeding from lactating ewes can be solved, more experiments are required to explain the effect of lactation on fertility. Compounds are now available which have a progestational effect on the genital tract and a conditioning effect on the hypothalamus. Ethinyl-nor-testosterone (ethisterone) which is active orally may prove superior to progesterone for this purpose, for progesterone has to be injected regularly and is less effective in conditioning the hypothalamus. No reports have yet appeared on the use of 6α-methyl-17α-hydroxyprogesterone acetate in sheep.

Use of Steroid Hormones to Prevent Embryonic Mortality

Total or partial embryonic mortality is a serious loss in agriculture, especially because animals for meat are now killed at lower liveweights and, therefore, more young animals must be produced per breeding female to produce the same tonnage of meat. Reference to work in laboratory animals has proved illuminating but not particularly helpful because results cannot be readily transferred to farm species. D'Amour *et al.* (1933) noted that extracts of the corpus luteum given from day one to ten of pregnancy improved the conception rate in rats and that the pups were heavier at birth although litter size in the pregnant animals was

not increased. Similarly, Nalbandov (1958) found that progesterone treatment did not affect litter size in rats, and Ulberg & Casida (1950) that the response of pregnant rabbits was very variable. In cattle of low fertility, œstrogen treatment has proved disadvantageous, but progesterone treatment improves the conception rate (Herrick 1953, Dawson 1954, Wiltbank *et al.* 1956, Johnson *et al.* 1958).

Neither rats nor cattle, in contrast to pigs and possibly sheep, seem to be adversely affected by dose rates of progesterone considered in excess of physiological levels (Naïbandov 1958).

Attempts to improve embryonic survival in pigs of normal fertility by the use of hormones have produced variable results. In some cases, particularly where high dose rates were used, the treatment appeared harmful to the growth and maintenance of the corpus luteum, especially if given during the first few days of pregnancy (Spies *et al.* 1959). However, improved embryonic survival has been reported during the first half of pregnancy in gilts when progesterone and œstrogen treatments have been combined (Reddy *et al.* 1958). In sheep high dose rates appear detrimental to the growth of the corpus luteum (Zimbelman *et al.* 1959) but the long-term effect on the maintenance of pregnancy has not yet been determined.

Even if the above improvements in fertility of farm animals are confirmed there remains the question of the wide variation in response of animals to the treatment and the problem of developing satisfactory methods of application. Single injections may prove satisfactory where high dose rates are tolerated, particularly now that long-acting forms of progesterone are becoming available. In pigs and possibly in sheep, where high dose rates are not tolerated and where repeated injections are probably impracticable, orally active forms may prove to be of greater benefit.

Control of Uterine Infections

Endometritis is a most important cause of sterility of cattle, and persistent uterine infections with pyometritis are known to be associated with a persistent corpus luteum. The synthetic hormone, diethyl stilbœstrol, has been frequently used for treating the condition. Alternatively, the œstrous period which results after the manual removal of the corpus luteum *per rectum* acts as a mechanism similarly clearing the uterus of infection (Rowson *et al.* 1953). It is known that conception rate improves if a heat period is allowed between parturition and insemination.

Susceptibility to many types of uterine infection in cattle is affected by ovarian hormones, the cow being resistant to experimental infections during œstrus but susceptible to infection when progesterone is being produced. We have compared the susceptibility of the cow, sheep, rabbit and rat to experimental uterine infections and found that both the cow and rabbit are susceptible when progesterone is active. On the other hand, the sheep appears relatively resistant to uterine infection at all stages of the œstrous cycle. The rat appears to have only moderate resistance to experimental uterine infections without significant differences during the œstrous cycle (Table 3). These species differences appear to be associated with the presence or absence of an acid-soluble fraction (A.S.F.), a carbohydrate-protein complex, of the uterine secretion. It is present at œstrus in the rat, during the luteal phase in the cow, during pseudopregnancy in the rabbit, but is absent *per se* in the sheep. When this material is present the uterus loses some of its resistance to experimental infections (Table 3).

Table 3

Species differences in the susceptibility to experimental uterine infections

Species	*Stage of cycle*	*Acid-soluble fraction*	*Bactericidal activity*
Rabbit	Œstrous	−	+++
	Luteal	+++	−−−
Cow	Œstrous	−	+++
	Luteal (late)	++	−−−
Sheep	Œstrous	−	++
	Luteal	−	+
Rat	Œstrous●	+++	+
	Luteal	−	+

●Spayed rats receiving œstradiol treatment
+ denotes present
− denotes absent

The mechanism of this resistance has been studied in the species mentioned but most fully in the rabbit. The resistance or susceptibility to infection is largely related to changes in the activity of the granulocyte system. When œstrogen predominates (and when the A.S.F. is absent), granulocytes, particularly neutrophils, rapidly infiltrate into the infected uterus where they reduce the infection before the logarithmic phase of growth is reached. On the other hand, when progesterone is active in the rabbit, the rate of leucocyte infiltration into the uterus is reduced and those leucocytes which reach the endothelium are predominantly lymphocytes rather than granulocytes; experimental infections progress more rapidly and become established.

These observations offer an explanation of the benefit of synthetic and natural œstrogens in clearing uterine infections. The stimulation of natural defence mechanisms is probably associated with an increase in the number of locally available granulocytes and the absence of mechanisms which interfere with phagocytosis.

REFERENCES
Allen D M & Lamming G E
(1959) University of Nottingham School of Agriculture Report
Armstrong D T & Hansel W (1958) *Fed. Proc.* **17**, 6
Clegg M T, Santolucito J A, Smith J D & Ganong W F
(1958) *Endocrinology* **62**, 790
D'Amour F E, D'Amour M C & Gustavson R G
(1933) *J. Pharm.* **49**, 146
Dawson F L M (1954) *Vet. Rec.* **66**, 324
Dutt R H
(1952) *J. Anim. Sci.* **11**, 792
(1953) *J. Anim. Sci.* **12**, 515
(1954) *J. Anim. Sci.* **13**, 464
Gordon I
(1957) *Agric. Rev.* **3**, 12
(1958) *J. agric. Sci.* **50**, 152
Hancock J. L. (1948) *Vet. Rec.* **60**, 513
Harris G W (1955) Neural Control of the Pituitary Gland. Physiol. Soc. Monograph No. 3. London
Hart D S (1950) *J. agric. Sci.* **40**, 143
Hays R L & Carlevaro C H (1959) *Amer. J. Physiol.* **196**, 899
Hays R L & VanDemark N L (1953) *Endocrinology* **52**, 634
Heap R B (1960) PhD Thesis, University of Nottingham
Herrick J B (1953) *Vet. Med.* **48**, 489
Hunter G L (1953) *J. Endocrin.* **10**, xiii
Hunter G L, Adams C E & Rowson L E (1955) *J. agric. Sci.* **46**, 143
Hutchinson J S M & Robertson H (1960) *Nature, Lond.* **188**, 585
Johnson K R, Ross R H & Fourt D L (1958) *J. Anim. Sci.* **17**, 386
Kammlade W G jr, Welch J A, Nalbandov A V & Norton H W
(1952) *J. Anim. Sci.* **11**, 646
Moore N W & Robinson T J (1957) *J. Endocrin.* **14**, 297; **15**, 360
Nalbandov A V (1958) *Ann. N.Y. Acad. Sci.* **71**, 580
Raeside J I & Lamond D R (1956) *Aust. J. agric. Res.* **7**, 601
Reddy V B, Mayer D T & Lasley J F
(1958) *Missouri agric. Exp. Sta. Res. Bull.* 667
Robinson T J
(1951*a*) *Biol. Rev.* **26**, 121
(1951*b*) *J. agric. Sci.* **41**, 6
(1954) *J. Endocrin.* **10**, 117
Rowson L E A (1951) *J. Endocrin.* **7**, 260
Rowson L E A, Lamming G E & Fry R M (1953) *Vet. Rec.* **65**, 335
Smythe R H (1943) *Vet. Rec.* **55**, 11
Spies H G, Zimmerman D R, Self H L & Casida L E
(1959) *J. Anim. Sci.* **18**, 163
Sykes J F & Cole C L
(1944) *Quart. Bull. Mich. agric. Exp. Sta.* **26**, 250
Ulberg L C & Casida L E (1950) *J. Anim. Sci.* **9**, 683
Wiltbank J N, Hawk H W, Kidder H E, Black W G, Ulberg L C & Casida L E (1956) *J. Dairy Sci.* **39**, 456
Yeates N T M (1949) *J. agric. Sci.* **39**, 1
Zimbelman R G, Pope A L & Casida L E
(1959) *J. Anim. Sci.* **18**, 1327

Meeting April 19 1961

The Transmission of Antibodies from Mother to Fœtus

Problems Concerning the Transmission of Immunity from Mother to Young

by Professor R W Rogers Brambell DSC FRS
(*Bangor, North Wales*)

Transmission of Immunity Before Birth

Transmission of immunity before birth in the rabbit, guinea-pig and rat takes place by way of the fœtal yolk-sac, not by the placenta. This is not surprising because this membrane corresponds to the yolk-sac of the chick, which has long been known to be the route of transmission in birds. Transmission in the primates cannot be by this route, since the yolk-sac is rudimentary. Consequently it has generally been assumed to be by way of the placenta in man, but as I pointed out a few years ago (Brambell 1958), there was no crucial evidence that this was so, and indeed, on comparative grounds, there was at least as good a case for assuming that it might be by way of the amniotic fluid and fœtal gut. I have repeatedly urged the need for experimental evidence on which to decide between these two theoretical alternatives. The first has been provided by Bangham, Hobbs & Terry (1958), using the monkey, and it indicates that the placenta is, indeed, the organ concerned. Thus the primate appears to differ from all other mammals so far studied in this respect. Perhaps, when we bear in mind the extraordinary diversity in the morphology of the fœtal membranes in mammals it is not surprising that it should be accompanied by a corresponding diversity in function. I emphasize this point because some physiologists are apt to oversimplify and to call all fœtal membranes, irrespective of their morphology, 'placenta', and even to expect them to function in a similar manner in different species.

Transmission After Birth in Rodents

In rats and mice most of the transmission of immunity takes place after birth and continues until near the end of lactation. It terminates somewhat abruptly about the nineteenth day of lactation in rats and the sixteenth day in mice. The period of cessation of transmission, when the intestine of the young animal becomes impermeable to protein molecules as such, is marked by a large increase in the alkaline phosphatase content of the entoderm cells. Moog (1953) had shown that this increase in alkaline phosphatase could be brought about prematurely by cortical steroids. Halliday (1959) has shown that cortical steroids, administered orally or parenterally, bring about prematurely not only the increase in alkaline phosphatase content of the cells, but the cessation of the transmission of immunity.

The very young rat, while still in receipt of passive immunity from the mother, is able to become actively immune. Halliday (1957) has shown that immunization at eleven days results in circulating antibody in three days, that is, at least four

days before the transmission of passive immunity begins to decline.

The uptake of the protein by the entoderm cells of the rat gut (as well as by those of the yolk-sac of the fœtal rabbit) appears to be by pinocytosis, as shown by both the light and the electron microscope (Clark 1959). Absorption therefore appears to be non-selective as between one protein and another in solution, a conclusion that is in accord with all our experimental evidence.

Release of the maternal globulin into the circulation of the fœtal or neonatal animal, on the other hand, appears to be highly selective in most animals, but not in all. In the rat it is selective in that γ-globulin is readily transmitted and β-globulin is not. Halliday & Kekwick (1960) have shown that hyperimmune anti-brucella agglutinins formed in rats are transmitted several times less readily than hyperimmune anti-salmonella agglutinins also formed in rats. Moreover anti-salmonella agglutinins formed in response to a primary immunization are transmitted less readily than those formed subsequently in response to hyperimmunization. This selectivity of the gut wall of the young rat or mouse resembles in many respects that of the fœtal membranes in transmission before birth, but it would be much too soon, on existing knowledge, to assume that the molecular basis of selection was necessarily identical in different species. Indeed there are clear indications of specific differences.

The selective nature of transmission in most animals was first noticed by Sir Percival Hartley (1951) and has been brought out in an already considerable literature from my own and several other laboratories. The phenomenon of selective transmission, however, merits far more attention. For example, it may go a long way to explain the confusion in the literature as to the relative concentrations of human antibodies in maternal and cord bloods at parturition. Whereas many maternal antibodies, including antitoxins, streptolysins, &c, are found in the cord serum at concentrations equalling or exceeding the maternal serum concentrations, other antibodies, notably complete isoagglutinins and typhoid 'O' agglutinins, are either absent from the cord blood or are present in very low relative concentrations.

Transmission in Ruminants

In ruminants there is no transmission before birth and that after birth is of very short duration. Antibodies are transmitted from the colostrum within thirty-six hours of birth and thereafter the neonatal gut is impermeable to them. Therefore, transmission is on a comparatively massive scale for a very short period. So far as the available evidence goes, including that of Bangham, Ingram, Roy, Shillam & Terry (1958) using trace-labelled serum proteins, transmission is not selective in ruminants, unlike other animals including man. The newborn calf displays at the time of transmission a marked proteinuria. Pierce (1959) has shown that it is mainly small molecular proteins which are eliminated in this way. Perhaps this proteinuria is the necessary corollary of the uptake, non-selectively, of so large an amount of protein over so short a period.

Finally, these cellular membranes across which transmission occurs – the fœtal yolk-sac, placenta, and the neo-natal gut – provide accessible and convenient membranes for the study of the mechanism of transmission by the cells. These cells absorb, select, transport and secrete whole protein molecules, some of which at least retain their biological activity during transit. They provide a wonderful opportunity, the advantages of which are not yet generally appreciated, for attempting experimentally to relate protein molecular structure and configuration to cell function.

REFERENCES

Bangham D R, Hobbs K R & Terry R J (1958) *Lancet* ii. 351
Bangham D R, Ingram P L, Roy J H B, Shillam K W G & Terry R J (1958) *Proc. roy. Soc.* Ser. B 148, 184
Brambell F W R (1958) *Biol. Rev.* 33, 488
Clark S L (1959) *J. biophys. biochem. Cytol.* 5, 41
Halliday R
(1957) *Proc. roy. Soc.* Ser. B 147, 140
(1959) *J. Endocrin.* 18, 56
Halliday R & Kekwick R A (1960) *Proc. roy. Soc.* Ser. B 153, 279
Hartley P (1951) *Proc. roy. Soc.* Ser. B 138, 499
Moog F (1953) *J. exp. Zool.* 124, 329
Pierce A E (1959) *J. Physiol.* 148, 469

The Exchange of Serum Proteins between Mother and Fœtus in the Rhesus Monkey [*Abridged*]

by D R Bangham MB (*London*)

The pattern of serum proteins of the human fœtus is different from that of the maternal serum, and the pattern changes during gestation and after birth, resembling the adult pattern several months after birth. Some proteins are found in the fœtal serum which are peculiar to the fœtus; some adult proteins do not occur in the fœtus. On the other hand many antibodies, 7 *S* γ-globulins, are transmitted to the fœtus. Gamma-globulin is found in fœtal serum at the 16th to 20th week and reaches a concentration similar to that in maternal serum at about 35 weeks. There is thus some sort of barrier between the two circulations, and at least one type of protein is known to cross it in one direction. However, little is known of the exchange of the other proteins common to both circulations. Thus three simple questions needed answering: (1) If maternal γ-globulin can reach the fœtus in the human, can any other (major) serum proteins do so? (2) What is their route of

transfer to the fœtus in the human? (3) What is the origin and fate of proteins in the liquor amnii?

The human placental system is unlike that of other orders; the yolk-sac and allantois are vestigial and at three months are functionless. At about the fourth month the fœtal capillary plexus in each placental villus is embedded in so-called primary mesenchyme, and covered with the cytotrophoblast and the syncytial or plasmodial trophoblast. After the fifth month, these two layers of cells are reduced to an extremely thin membrane. In the fully grown human placenta, freely circulating maternal blood and the fœtal capillary system are separated by some 6–10 sq m of syncytial membrane, in many places scarcely 1μ thick. Only among some of the primates are comparable placental systems found. The catarrhine placenta of the rhesus monkey comes very closely to resemble the human placenta (Amoroso 1952).

We have used rhesus monkeys to study the three questions on protein transfer in the primate. The gestation period of the rhesus monkey is some five and a half months, and those we used were about four months pregnant. We used isologous whole serum trace-labelled with ^{131}I in these experiments, as we were interested in the comparative transmission of different serum proteins rather than in exact quantitative measurement of transfer of individual ones. The serum (0·2–0·3 ml, 15–25 mg of protein) was labelled with 1–1·5 mc of ^{131}I by the jet method or the iodine monochloride method of McFarlane (1958). There is much evidence that those proteins, labelled under carefully controlled conditions at an average of one atom of ^{131}I per molecule, or 'less', behave metabolically like unlabelled molecules. In studies of protein transmitted across a membrane it is likely that the amount of labelled protein measured represents at least a minimum of the total amount actually transmitted.

Three sets of experiments were performed. In the first, fresh maternal serum was labelled and reinjected intravenously into the mother. Maternal serum and liquor were taken at intervals and a Cæsarean section performed at eight or twenty-four hours in order to collect fœtal serum. The proteins in each sample of serum and liquor were separated by column electrophoresis (which gives a serviceable, if rough-and-ready, separation of proteins) and the γ-globulin was isolated by chromatography on DEAE cellulose.

The pattern of proteins separated by column electrophoresis in a sample of the labelled serum used for the dose corresponds quite closely with the pattern of radioactivity. In the fœtal serum taken eight hours after injecting labelled maternal serum, radioactivity was present in the albumin peak and also in the γ-globulin position; in fœtal serum taken twenty-four hours after the dose there was a similar pattern, but there was more radioactivity in the γ-globulin region. In the dose the ratio of counts in the albumin to counts in the γ-globulin (isolated chromatographically) was about 15:1. In the fœtal sera the ratio was more like 1 : 1. That the second radioactive peak was due to γ-globulin was shown by chromatography on DEAE cellulose. Moreover, the amount of radioactivity in this γ-globulin accounted for nearly all the radioactivity in the globulin region eluted from the electrophoretic columns.

In the liquor amnii there was a lot of radioactivity in the albumin region by eight hours, but little in the globulin region, and by twenty-four hours there was little change. The liquor amnii contains fifteen to twenty times less total protein per ml than serum; many but not all of the main serum proteins are present, but in different relative proportions. The chief difference is due to a particular globulin which we have found only in liquor in monkeys (Bangham *et al.* 1961); it is the major protein constituent in mid-pregnancy but diminishes in concentration considerably at the end of pregnancy. The amount of γ-globulin is small, less than in fœtal serum at this age, and the specific activity of the γ-globulin in the liquor was lower than that in the fœtal serum at twenty-four hours.

These experiments showed, then, that γ-globulin and a little albumin were selectively transmitted to the fœtal serum. Albumin passed readily into the liquor together with some globulins, but the specific activity of the γ-globulin in the latter was lower than the specific activity of the γ in the fœtal serum.

In the second type of experiment similar labelled fresh maternal serum was injected directly into the liquor amnii. Samples of maternal blood were taken, and a Cæsarean section performed at eight or twenty-four hours. Although the specific activity of the γ-globulin in the liquor was some 500 times greater than that found in the previous experiments, the fœtal serum contained insignificant radioactivity in the γ-globulin; a little activity was found in the albumin region. The maternal serum contained radioactivity in the albumin and a little in the globulin region.

The stomach and gut of the fœtus were washed out and the ileum was found to contain all the main labelled proteins. There was no doubt, then, that although the fœtus had swallowed the proteins it had not absorbed any significant quantity into its blood.

The conclusions from these experiments are that the transfer of γ-globulin and albumin from the mother to the fœtus is transplacental and not *via* the liquor amnii. These confirm the implica-

tions of the critical observation of Wasz-Höckert *et al.* (1956) that serum of 5 infants born with œsophageal or œsophago-tracheal atresia contained diphtheria antitoxin in the same concentration as was present in their mothers' serum. Another conclusion is that at least some of the proteins of the liquor can return to the mother's circulation.

We were then interested in the possibility of the return of some proteins from fœtal blood to the mother, and in the contribution the fœtus makes to proteins in the liquor (Bangham *et al.* 1960). To investigate this we needed access to the fœtus but without the interruption of pregnancy. It was found possible to do this at open operation, and in two monkeys a dose of ^{131}I-labelled fœtal serum was injected either intravenously or intraperitoneally at operation. With direct vision we could make sure that there was no leak from the injection site. Later, we found it possible to implant a cannula in the peritoneal cavity of a fœtus at open operation. The fœtal skin was closed round the cannula to make a leak-proof seal. The cannula was brought out through the incision in the uterus and the end was sealed and implanted under the skin of the mother's flank. The uterus was sown up and the liquor amnii put back. A week later some serum – which had been taken from the fœtus at operation – was labelled with ^{131}I and injected down the cannula.

Two such monkeys were prepared. Samples of liquor and maternal serum were taken at intervals after injection of the labelled fœtal serum. The results from all four monkeys were closely similar. Radioactivity was present in maternal serum taken twenty-four hours later in the albumin region and a little in the γ-globulin region – which was confirmed by chromatography. The same general findings were obtained in maternal samples removed four and eight days later. Samples of liquor showed insignificant quantities of labelled protein in the first twenty-four hours (we took this as evidence that there had been no leak from the wound in the fœtus). By two days, labelled albumin appeared in the liquor with a specific activity exceeding that in the maternal serum; it must be presumed to have come from the fœtus. There was, however, no radioactivity in the globulin region, so we think that this represented the trace quantities of proteins (mostly albumin) excreted in fœtal urine – demonstrable also by immunoelectrophoresis. At four days, radioactivity was also present in the globulin region.

The conclusion from these experiments is that albumin and a little γ-globulin can return, across the placenta, into the maternal circulation. Furthermore, the fœtus seems to contribute very little of its serum proteins to the liquor (or if it does contribute more than a trace, the rate must be very slow).

These experiments observe only the movement of relatively small absolute amounts of the major proteins of serum. No attempt was made to measure the many individual constituents present in serum in low concentration, or the movements of trace amounts of proteins; each one will have to be studied individually. We have some other support for the proposition that transferrins, for instance, do not exchange between mother and fœtus or between fœtus and liquor (Bangham *et al.* 1961). Rhesus monkeys have a number of genetic variants of transferrins. Starch gel electrophoresis of groups of maternal and fœtal serum and liquor show that some variants occurring in the fœtal serum do not occur in maternal serum, while the maternal variants do not occur in the fœtal serum. The pattern of variants in the liquor always corresponds with that of the maternal serum. Immunoelectrophoresis in agar shows the common antigenicity of the variants and, with studies of ^{59}Fe binding, confirms the similarity of the pattern in maternal serum and liquor.

The concept of a cell layer selectively transmitting albumin and γ-globulin in one direction is not new. The epithelium of the mammary gland allows a lot of serum γ-globulin and a little serum albumin through into milk (trace quantities of other serum proteins are also found in milk). The gut of the suckling rat selects and transmits γ-globulin much more easily than albumin. The process of transmission has been studied by Clark (1959) at a cellular level, in the gut of suckling rats, using fluorescent-labelled antibody and specific protein antigens. He demonstrated that mixtures of proteins were imbibed by pinocytosis by the brush border of the endothelial cells, and that γ-globulin remained selectively unaffected (antigenically) during the movement of the coalesced droplets towards the base of the cell. The syncytial trophoblast of the rhesus placenta, however, is apparently able to transmit them either way; moreover it exercises some discretion in the relative amounts of albumin and γ-globulin that are transmitted. This two-way process requires careful confirmation and study at a cellular level.

In summary, some maternal albumin is transmitted to the fœtus, although not so easily as γ-globulin, as was suggested by Gyllenswärd & Josephson (1957). Little, if any, of the other major serum proteins cross the placenta. The transmission of γ-globulin is truly transplacental in the primate, and not *via* the liquor. Proteins in the liquor amnii come from and return to the maternal circulation presumably across the chorion and amnion. The fœtus probably contributes only trace quantities. Both albumin

and a little γ-globulin can selectively be returned *via* the placenta to the maternal circulation.

This work was carried out in collaboration with Mr K R Hobbs and Dr D E H Tee.

REFERENCES
Amoroso E C
(1952) In: Marshall's Physiology of Reproduction, London; 2, 127
Bangham D R (1960) *J. Physiol.* 153, 265
Bangham D R, Hobbs K R & Tee D E H
(1960) *Lancet* ii, 1173
(1961) *J. Physiol.* 158, 207
Clark S L jr (1959) *J. biophys. biochem. Cytol.* 5, 41
Gyllenswärd C & Josephson B
(1957) *Scand. J. clin. Lab. Invest.* 9, 21
McFarlane A S (1958) *Nature, Lond.* 182, 53
Wasz-Höckert O, Wager O, Hautala T & Widholm O
(1956) *Ann. Med. exp. Fenn.* 34, 444.

Proteinuria in the Newly Born

by A E Pierce PhD MSC FRCVS DVSM (*Cambridge*)

The newly born of certain species acquire a passive immunity *post partum* from ingested maternal colostrum. Evidence is presented which correlates the special permeability of intestinal mucosa to protein macromolecules, which obtains at this time, with a concomitant proteinuria. The present study has been carried out on the calf, although evidence is shown that a similar mechanism may operate in other species.

The Mechanism of the Passive Transference of Immunity from the Cow to the Newly Born Calf

In most animals of economic importance, particularly the ungulates, protective antibodies are acquired *post partum* as the result of suckling colostrum; the horse, dog and cat also fall into this category. Antibodies present in the colostrum at high titre pass readily across the mucous membrane of the small intestine; they are probably taken into the epithelial cells by a process of pinocytosis (Clark 1959) and enter the lacteals of the villi eventually draining through the thoracic lymph duct into the jugular vein and so into the general circulation (Comline *et al.* 1951). Therefore, compared with man and other animals such as the rabbit and guinea-pig which acquire their passive antibody *in utero*, the ungulate at birth is immunologically unstable. Not only is the plasma devoid of antibody, but on electrophoretic analysis is agammaglobulinæmic. Therefore, in many animals the colostral proteins have great significance for the survival of the offspring and are responsible for establishing its early postnatal immunological stability.

The Origin and Distribution of the Major Colostral Proteins

Fig 1A shows the electrophoretic pattern for calf serum shortly after birth and before suckling. The pattern for the same calf forty-eight hours after suckling is shown at Fig 1D, by which time the calf has acquired, passively from the colostrum, just over 50% of its total serum protein and from a state of agammaglobulinæmia has become hypergammaglobulinæmic.

There is now strong evidence that the maternal blood plasma is the site of origin for the immune lactoglobulin, the protein component with antibody activity, in the colostrum. There is a drop in the level of the circulating γ-globulin in the pregnant cow at the time when the immune lactoglobulin is being concentrated in the mammary gland (Fig 2).

Immune serum, if given passively to a pregnant cow during this period of pregnancy, is concentrated up to thirteen times, by a remarkable process of which we know almost nothing, in the mammary gland (Blakemore & Garner 1956, Garner & Crawley 1958).

Studies by Askonas, Campbell, Humphrey & Work (1954) in the rabbit and goat, and by Larson & Gillespie (1957) in cattle, failed to show the incorporation of radioactive aminoacids into the immune lactoglobulin. However, they were incorporated into the casein and β-lactoglobulin components (Askonas, Campbell & Work 1954, Askonas *et al.* 1955). Therefore these two proteins characteristic of milk differ from immune lactoglobulin in being synthesized in the mammary gland; with the immune lactoglobulins they form the major protein components in the colostrum (*see* Fig 1B, C).

The Fate of the Colostral Proteins Within the Newly Born Calf

(*a*) *Casein and immune lactoglobulin:* Gastric rennin which is active at birth precipitates the casein (*see* Fig 1B); therefore, it is the immune lactoglobulin together with the β-lactoglobulins and lactalbumin – the colostral whey proteins (*see* Fig 1C) – which are available for absorption in the small intestine during the vital hours when the mucosa is permeable to undegraded macromolecules.

The facile absorption of the immune lactoglobulin and its accumulation in the circulation has already been shown (Fig 1), and the effect of this in terms of antibody activity has been repeatedly studied with a wide range of antigens in the seventy years since Ehrlich (1892) showed the passive transference of immunity to offspring from immune mice. These observations have been confirmed in more catholic terms recently in biophysical studies on the proteins themselves (Pierce 1955) and the importance of the immune lactoglobulin for the survival of the calf has been established beyond doubt by the work of Ingram and his colleagues (Ingram *et al.* 1953, Ingram *et al.* 1956).

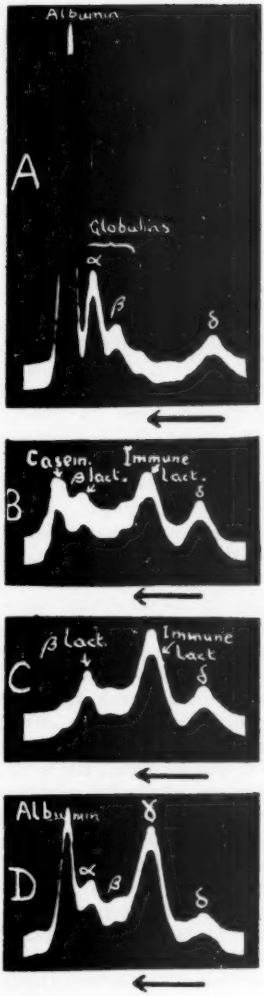


Fig 1

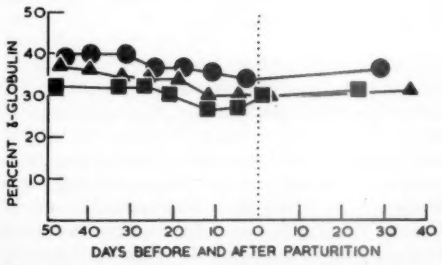


Fig 2 *Electrophoretic analysis showing the decrease in the serum γ-globulin levels of three cattle approaching parturition*

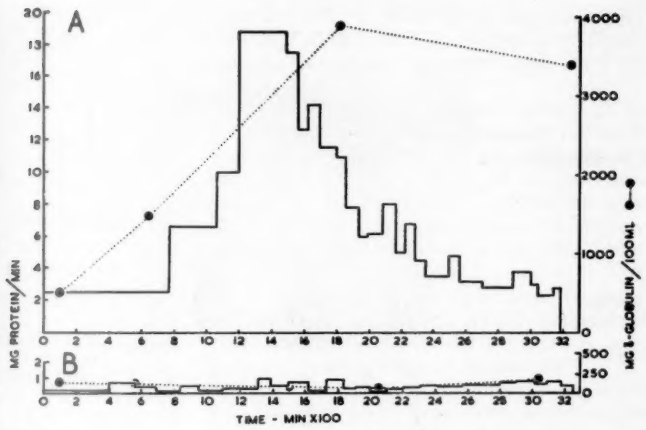


Fig 3

Fig 4A

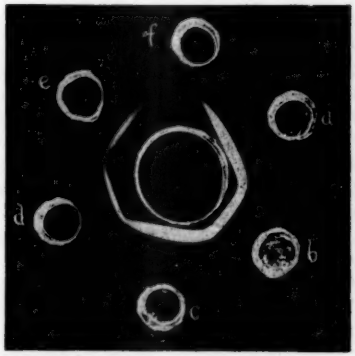


Fig 4B

Fig 1 *Electrophoretic patterns in phosphate buffer pH 8·0, I (ionic strength) = 0·2 for,* A, *newly born calf serum before suckling,* B, *bovine colostrum,* C, *bovine colostral whey, and* D, *calf serum forty-eight hours after feeding colostrum, showing at γ the passively acquired immune lactoglobulin component*

Fig 3 A, *Electrophoretic analysis showing the rise in mg γ-globulin/100 ml serum (passively acquired colostral immune lactoglobulin) in a calf fed on colostrum and the renal protein excretion rate in mg protein/min.* B, *The same analyses for a calf fed glucose saline. Time* O = *Birth*

Fig 4 A, *Immuno-electrophoresis in agar gel showing at* (a) *the precipitin band developed between a β-lactoglobulin fraction and an anti-β-lactoglobulin rabbit serum together with* (b) *the agar stained for protein.* B, *The line of reaction identity between rabbit anti-β-lactoglobulin serum in centre well and* (a) *β-lactoglobulin,* (b) *colostrum,* (c) *urine,* (d) *lymph, and* (e & f) *calf serum. Samples* (c), (d) & (e) *were derived from a calf fed colostrum and during the period of gut permeability;* (f) *was serum taken before feeding colostrum*

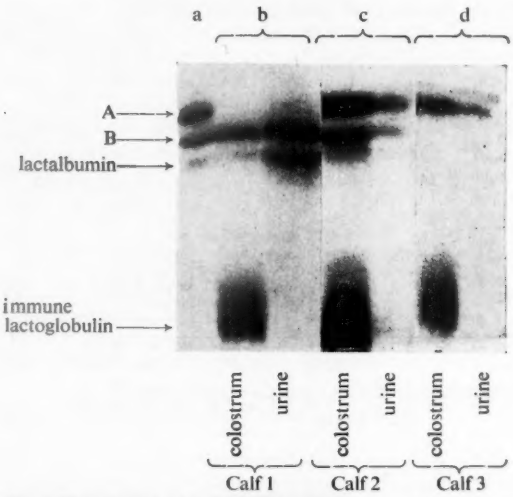


Fig 5 *Starch gel electrophoresis showing at* (a) *control β-lactoglobulin AB, and at* (b), (c) *and* (d) *the genetic types of β-lactoglobulin B, AB & A in colostrum fed to calves 1–3, together with their associated urine protein*

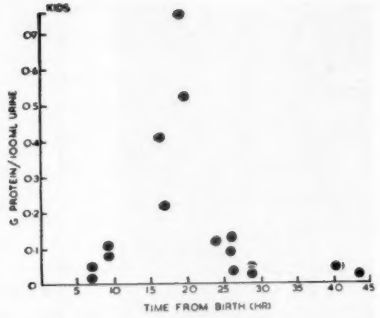


Fig 6 *The protein concentrations in urine recovered from newly born kids fed on maternal colostrum*

The work of Brambell and his colleagues has stimulated interest in the selective absorption of homologous and heterologous proteins with particular reference to the newly born rabbit, chicken and rat (*see* Brambell 1958). It is in this context that proteins other than the immune lactoglobulins will be considered.

(*b*) *β-lactoglobulin and lactalbumin:* In 1924 Smith & Little, and Howe, showed the development of a proteinuria, largely an albuminuria, though globulins were also noted, after the calf suckled colostrum. We repeated this work and found that the duration of gut permeability, as measured by an increasing concentration of immune lactoglobulin in the plasma of the calf, coincided with the period of proteinuria. There appeared to be a special, though transient, permeability common to both intestine and kidney. Fig 3A shows the protein excretion rate for a calf fed colostrum. There is a rising rate of protein excretion with concentrations in the urine exceeding 2 g/100 ml. This is followed by a period, about thirty-five to fifty hours *post partum*, when the excretion rate rapidly drops to normal. No proteinuria developed either when the colostrum was replaced with glucose saline (Fig 3B) or as the result of the intravenous injection of large volumes of serum protein (Pierce 1961). When the protein in the urine from calves fed colostrum was examined electrophoretically, although the pattern was variable, it showed characteristically a major fast component with a mobility comparable with albumin; the salting-out characteristics were also compatible with serum albumin (Pierce 1959).

Further examination in the analytical ultracentrifuge showed a significant discrepancy between the sedimentation constants for the urinary proteins and those for serum albumin, or any of the other serum proteins of the newly born calf (Pierce & Johnson 1960). All the urinary protein showed values of 3 or less Svedberg units (*S*) compared to values of 4 *S* or more for all the serum proteins. However, proteins with a sedimentation behaviour similar to those in the urine were found to comprise most of the colostral protein apart from the 6·5 *S* immune lactoglobulin component (Pierce & Johnson 1960). Therefore the available evidence suggested that, in addition to the immune lactoglobulin, the β-lactoglobulin and lactalbumin also were absorbed from the intestine; and that fractionation within the kidney cleared the smaller molecular weight proteins from the circulation, probably by glomerular filtration, and retained the larger molecular weight immune lactoglobulins.

The Identity of the Urine Proteins

Two further experiments were carried out to study the contribution of the β-lactoglobulins to the proteinuria.

(*a*) *Immunological methods:* A rabbit antiserum was prepared against a crystalline β-lactoglobulin (prepared as described by Aschaffenburg & Drewry 1957*a*). The specificity of the precipitin band for the β-lactoglobulin was examined by immuno-electrophoresis (Fig 4A) and the absence of any cross-reaction with normal bovine serum proteins confirmed. Fig 4B illustrates the line of

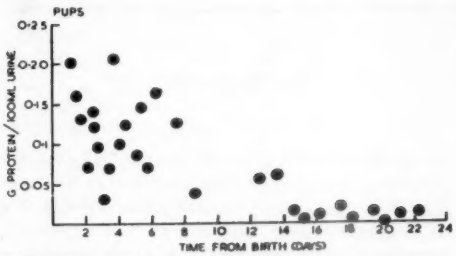


Fig 7 *The protein concentrations in urine recovered from newly born puppies fed on maternal colostrum*

reaction identity obtained using this antiserum against β-lactoglobulin, whole colostrum, the urine derived from a suckling calf during the period of gut permeability and consequent proteinuria, and against the lymph and serum after suckling. It is clear that using a more sensitive immunological method, protein, such as the β-lactoglobulin, can be detected in the general circulation which was not revealed previously by electrophoretic or ultracentrifugal analysis.

(*b*) *Starch electrophoretic methods:* Aschaffenburg & Drewry (1955, 1957*b*) have shown there are two major β-lactoglobulins which are genetically inherited and may be identified by their electrophoretic behaviour. By starch electrophoresis these may also be distinguished from serum albumin (Pierce 1960). Colostra were collected from cows showing the genetic varieties of β-lactoglobulin A, AB and B and each was fed to one of three calves. A comparison was then made between the β-lactoglobulins fed and the protein recovered from the urine of the calf.

Fig 5 shows the identity of the β-lactoglobulins fed and those recovered from the urine. The results also suggest that the lactalbumin is dealt with in a similar manner. The selectivity of the renal clearance is shown, there being little evidence of immune lactoglobulin in the urine, and the major contribution of the β-lactoglobulins to the proteinuria is confirmed.

Proteinuria in Other Species

Proteinuria in other species where the gut is permeable *post partum* to protein macromolecules is being examined. McCarthy & McDougall (1949, 1953) have already shown a proteinuria in the newly born lamb, and we have confirmed this and extended our observations to the goat and dog. The protein values for urine collected from goats are shown in Fig 6 and are closely similar to those obtained in sheep and calves. The period of permeability of the intestine of the newly born pup is ten days (Brambell 1958) as opposed to some twenty-four to thirty-six hours in the goat, lamb and calf; a moderate proteinuria persists for a much longer period in the pup (Fig 7), finally dropping to minimal values fourteen days *post partum*.

There is ample evidence that the gut of the newly born human infant is not readily permeable to undegraded colostral protein associated with antibody activity. However, up to 200 mg of protein, based on values for nondialysable nitrogen, have been shown for urine collected after suckling and up to 70 hours of age. This urinary protein shows similarities in terms of electrophoretic mobility and ultracentrifugal behaviour with protein other than immune lactoglobulin which is present in human milk. Work is proceeding to examine the origin of these proteins.

In conclusion evidence has been shown supporting the absence of a high degree of selectivity by the intestinal mucosa of the newly born of several species of animals which acquire their antibody passively *post partum* from ingested maternal colostrum. This does not preclude some degree of selectivity and certain experiments reported elsewhere suggest that proteins other than the immune lactoglobulins are not absorbed so readily (Pierce 1961). However, sufficient of these low molecular weight proteins are absorbed to give rise to marked, though transient, proteinuria arising when these proteins are ingested and persisting during the period when the intestine remains permeable to undegraded protein.

REFERENCES

Aschaffenburg R & Drewry J
(1955) *Nature, Lond.* **176**, 218
(1957*a*) *Biochem. J.* **65**, 273
(1957*b*) *Nature, Lond.* **180**, 376

Askonas B A, Campbell P N, Humphrey J H & Work T S
(1954) *Biochem. J.* **56**, 597

Askonas B A, Campbell P N & Work T S (1954) *Biochem. J.* **58**, 326

Askonas B A, Campbell P N, Godin C & Work T S
(1955) *Biochem. J.* **61**, 105

Blakemore F & Garner R J (1956) *J. comp. Path.* **66**, 287

Brambell F W R (1958) *Biol. Rev.* **33**, 488

Clark S L jr (1959) *J. biophys. biochem. Cytol.* **5**, 41

Comline R S, Roberts H E & Tichen D A
(1951) *Nature, Lond.* **167**, 561

Ehrlich P (1892) *Z. Hyg. InfektKr.* **12**, 183

Garner R J & Crawley W (1958) *J. comp. Path.* **68**, 112

Howe P E (1924) *J. exp. Med.* **39**, 313

Ingram P L, Lovell R, Wood P C, Aschaffenburg R, Bartlett S, Kon S K, Palmer J, Roy J H B & Shillam K W G (1956) *J. Path. Bact.* **72**, 561

Ingram P L, Lovell R, Wood P C, Aschaffenburg R, Bartlett S, Kon S K, Roy J H B & Sears H J (1953) *XIII Int. Dairy Congr.* **3**, 1369

Larson B L & Gillespie D C (1957) *J. biol. Chem.* **227**, 565

McCarthy E F & MacDougall E I
(1949) *Nature, Lond.* **164**, 354
(1953) *Biochem. J.* **55**, 177

Pierce A E
(1955) *J. Hyg., Lond.* **53**, 247
(1959) *J. Physiol.* **148**, 469
(1960) *Nature, Lond.* **188**, 940
(1961) *J. Physiol.* **156**, 136

Pierce A E & Johnson P (1960) *J. Hyg., Camb.* **58**, 247

Smith T & Little R B (1924) *J. exp. Med.* **39**, 303

Meeting May 17 1961

Iron Metabolism

Iron Deficiency in Man and Animals

by J L Stafford MB (*London*)

The purpose of this communication is twofold. It is to draw attention to the physiological importance of iron other than that functioning in hæmoglobin; secondly, to refer to some of the other activities which may be ascribed to body iron. Only a few points can be mentioned and, for a fuller account of iron metabolism and iron deficiency anæmia in human practice, the review by Davidson (1960) serves as a most excellent survey.

The current understanding of iron absorption, transport and storage in the human is largely based on animal experiments. Fortunately the physiological sequence in man and the higher mammals appears to be sufficiently similar to permit direct comparison though there is one major discrepancy: iron deficiency, *as routinely expressed by low hæmoglobin levels*, is very uncommon among adult animals and yet is common in the human female. Indeed, except for stock reared on iron-deficient soil, such as cattle developing Florida salt sickness, or deliberately deprived of iron as are the intensively milk-fed Dutch veal calves, or reared in artificial surroundings to produce piglet anæmia, naturally available iron is so abundant that its lack apparently presents no problem in animal husbandry. The paradox is the relatively frequent deficiency in the adult human female whose body iron economy is precarious because of the coincidence of artificial dietary convention and regular menstrual loss.

The usual assessment of iron deficiency, by reference to hæmoglobin concentration in the circulating red cell, remains entirely valid, but it is now clinically apparent that not all iron lack is so expressed – the possibility exists of a significant body deficit with a normal or near normal circulating hæmoglobin concentration. Such cases in human clinical practice show some of the symptoms of iron deprivation and are cured by its exhibition: the possibility may exist of a similar situation in animals, hitherto ignored because a finding of a normal hæmoglobin seemed to preclude any such state.

The iron absorptive mechanism in animals and man is relatively inefficient for only some 10% of dietary iron is assimilated in the normal state. This may, however, increase as much as threefold, if the subject is avid as a result of severe depletion. By inference it is calculated that the 70 kg human possesses some 5 g of elemental iron in his body distributed as 3 g in circulating hæmoglobin, 1 g in myoglobin and the various iron-dependent respiratory enzymes and 1 g as ferric-protein complexes in store or in transit within the plasma: an adult male requires to absorb some 1·25 mg daily to maintain equilibrium, whereas the menstrual loss of the female doubles her requirement so that she will need a total of 20–25 mg of dietary iron to allow for actual assimilation of 2·5 mg iron *per diem*. Table 1 emphasizes that whilst there is a reasonable amount of iron in a variety of natural foods, the standard 'milk, meat and two veg.' of the urban dweller is suboptimal and leaves little or no leeway for the housewife. Crude molasses, marketed as black treacle, is the best natural source and its use to control lactic acid production in silage fortuitously provides the stock-fed animal with an ample supply.

Table 1
Amount of iron in natural foods (mg/kg)

Animal		*Plant*	
Liver	121	Molasses	475
Egg yolk	72	Parsley	192
Kidney	65	Rice bran	160
Corned beef	40	Soya flour	121
Beef steak	25	Cabbage	6
Cow's milk	1	Potatoes	8

In vertebrate physiology, iron metabolism has one unique feature whereby control of body levels depends solely on absorptive selection: unlike all other body minerals there is no natural regulatory excretory mechanism, as loss by bile, sweat or hair is minimal. A constant supply must therefore entail some form of 'storage' facility together with circulatory interchange and the cycle may be arbitrarily divided into intake, distribution and intracellular immobilization as shown in the alliterative scheme in Fig 1.

To serve *actively* for oxygen transfer, iron is chelated in the ferrous form with porphyrin prosthetic groups: as hæmoglobin or myoglobin conjugates which can combine reversibly with oxygen, or in the redox systems of cytochromes and respiratory enzymes where its valence alternates between the ferrous and ferric forms during electron transfer. Such iron may be more easily available in these ferrous chelates because of its superficial and loosely linked position relative to the prosthetic group. Alternatively, iron in transit

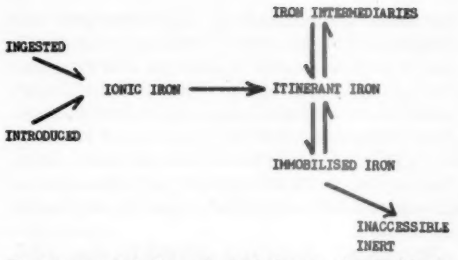


Fig 1 *Iron metabolic cycle. Ionic iron is absorbed in the ferrous form; itinerant iron is the ferric-transferrin complex; iron intermediaries (ferrous-porphyrin chelates) are largely hæmoglobin; immobilized iron is the ferric-apoferritin store which may possibly become inert as hæmosiderin*

or immobilized intracellularly exists in the ferric form as a protein complex – transferrin, ferritin and hæmosiderin in man. To imply that such iron is thus *inert* is not strictly accurate, though its release from hæmosiderin is somewhat tardy: it is not, however, directly available for oxygen transfer, possibly because the ferric ions are not sited superficially but as an integral part of the much larger protein moiety. Some 'active' iron probably does exist in the ferric form in the succinic dehydrogenases and in xanthine oxidase (Beutler & Blaisdell 1958, 1960) and the arbitrary designation of valence to such a reactive moiety is a largely casuistic attempt to express in chemical terms a very changeable physical state.

In Fig 2 is depicted the currently accepted cycle in the human adult, with three clinical syndromes in which the normal sequence is altered shown in stippled frames. The bulk of the iron circulating, amounting to some 20–25 mg per day, is derived from the normal breakdown of about 0·8–1% of the total red cell mass and this characterizes the closed-circuit economy by which iron is continually re-utilized. To this is added a small increment from myoglobin catabolism and iron-containing enzyme degradation. A second component of this cycle is the release of intracellular 'storage' iron present as ferric protein complexes: it is a reasonable presumption that this maintains equilibrium and is capable of making good any temporary deficiency. Thirdly, there is the small dietary intake of some 1–2·5 mg daily to balance the minimal loss by 'wear-and-tear'. At every point in this cycle where ionic iron crosses a cell membrane, valence change is presumed: within the cell and in the plasma, iron in transit is in the ferric form.

Clinical Notes

The dominant role in human iron metabolism played by hæmoglobin has tended to overshadow the equally vital functions of the iron-dependent enzyme systems. Thus, in clinical practice, iron deficiency has become synonymous with hæmoglobin deficiency and has been expressed solely in terms of anæmia, and the possibility of iron deficiency existing without a demonstrable drop in hæmoglobin concentration and without anæmia has been overlooked. There is now, however,

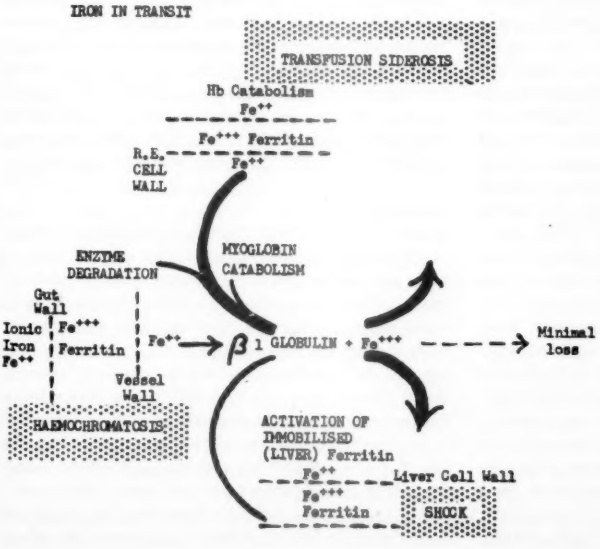


Fig 2 *Schematic diagram of the iron metabolic cycle in man. The dotted lines imply cell membranes at which point there is a valency change as the iron crosses. The stippled blocks refer to three clinical situations in which that particular part of the cycle is upset. The central point of all transference is the β-globulin–transferrin*

growing realization that this parameter is not an infallible index of iron sufficiency in human physiology and, as other parameters become capable of expression, unsuspected iron deficiency may yet be found as an explanation of obscure clinical syndromes.

From the point of view of physical work sedentary function is possible without much difficulty with the hæmoglobin concentration as low as 50% (7·5 g/100 ml). For years it has been apparent that the hæmoglobin deficit of Addisonian pernicious anæmia, without iron shortage, permits of physical function to a much lower level of hypoxia than is possible with simple iron deficiency states. The symptomatology of the latter is not wholly the result of circulatory hypoxia but rather a combination of this together with tissue enzymic depression whereby reduction-oxidation at the cellular level becomes inefficient. Prior to the last decade, response to oral iron therapy was sufficiently slow to make it impracticable to discern between the effect of hæmoglobin rise and the remission of nonhæmic symptoms – lassitude, buccal epithelial degradation, dysphagia, koilonychia, psychical disturbances and undue motor fatigue. With the introduction of parenteral iron therapy a discrepancy has been revealed, for there may be substantial subjective improvement within a day or so whilst the hæmoglobin concentration is yet low (Jennison & Ellis 1954).

In the past one has been prone to regard subjective symptoms, especially those associated with emotional instability in the female, as functional: hæmoglobin assessment has been the only acceptable objective evidence of abnormality. The finding of these iron deficiency symptoms in the presence of a normal hæmoglobin concentration is thus of particular interest.

Among 200 dental patients referred from the Royal Dental Hospital for post-extraction bleeding, where no local cause could be identified, 19 women had marked capillary fragility directly associated with iron deficiency anæmia and responding completely to iron therapy: a further 5 with identical symptoms but *a completely normal hæmoglobin level* were also cured by intravenous iron injection. Both groups, with or without anæmia, had subnormal plasma iron levels of less than 80 μg/100 ml.

A second group of patients, also women, were referred to St George's Hospital with angular stomatitis, glossitis or chronic buccal ulceration. In 7 such patients with normal hæmoglobin levels, the plasma iron concentration was significantly reduced: the debilitating local condition, which in one patient had persisted for five years, cleared within a week or ten days of parenteral iron therapy.

Thirdly, a single example of gross koilonychia has been investigated in a middle-aged man suffering from chronic tuberculosis. Admittedly the hæmoglobin concentration was low for a man (11·4 g/100 ml) but nowhere near the level usually found in the glossitis-dysphagia-koilonychia syndrome. None the less the plasma iron level was 47 μg/100 ml. He had a mild paranoia. Intravenous iron promptly relieved the latter and nail growth reverted to normal over the subsequent few months.

Sideropenic dysphagia (Waldenström 1946, Henderson 1954) is a term given to pharyngo-œsophageal spasm without apparent organic cause, in the presence of a low plasma iron: one example of this disability in a woman with a normal hæmoglobin has been studied and a complete clinical cure resulted from intravenous iron therapy.

A feature of iron deficiency states in women is the intensification of menorrhagia as a result of the anæmia which it induces. In such patients there is occasionally an underlying psychogenic disturbance and it is often difficult to discern whether the condition improves as a result of iron therapy or because of the greater interest taken in the patient's welfare. Two women with normal hæmoglobin levels but plasma iron levels respectively of 52 and 24 μg/100 ml and suffering from severe menorrhagia have shown substantial improvement with intravenous iron. The follow-up period, however, is too short for confident assessment.

Each of these 16 patients shows some evidence of a sub-optimal body iron concentration masked by a normal hæmoglobin, and one may presume their symptoms to be due to intracellular enzyme deficiency readily corrected by parenteral iron. In the same context it is relevant to mention the gastric hypochlorhydria long considered to be the cause of iron deficiency but now largely accepted to be its effect. This also responds to treatment and gastric function may recover, albeit slowly, once the iron deficit is corrected.

Discussion

Within the adult human iron is largely committed to hæmoglobin synthesis, whilst some 10% of this amount enters the myoglobin molecule. Hæmoglobin turnover is considerable as red cell survival is limited to one hundred and twenty days, some 25 mg of released ionic iron being transported and re-used daily to cover normal replenishment of the red cell mass. Myoglobin turnover is supposedly much slower, as assessed in the rabbit (Indovina 1951) though this has not yet been studied in the human. One may speculate that in times of absolute iron deficiency, reduction of circulating hæmoglobin may be accompanied by a parallel reduction in myo-

globin – this latter contributing to motor inefficiency. Over sixty years ago Greig (1898) observed that the female salmon takes no food when swimming back to the spawning ground; this considerable period covers the production of eggs which contain a total of elemental iron greater than the estimated stores of the fish and he suggested that myoglobin stocks were also utilized as the hæmoglobin level did not appear to fluctuate.

The other forms of body iron are also presumed to be freely labile. Apart from iron actually present in certain enzyme molecules, it may also be an essential component of co-factors to non-iron enzymes (Dickman & Cloutier 1950) and many apparently unrelated enzyme systems can thus be rendered inefficient by its absence. The parts played by the ferric-protein complexes, ferritin, hæmosiderin, and transferrin, have yet to be completely assessed. Ferritin, which is ordinarily present as both an intracellular transport complex and as a storage molecule, may exist in more than one form. This metal protein complex carries iron in the ferric form: in the duodenal mucosa and in the cells of the reticulo-endothelial system, its presence is transitory and the iron swiftly transferred to the plasma. On the other hand, in the areas regarded as 'stores', notably the liver, apparently identical molecules must hold ferric ions for considerable periods. These remain in solution and are still readily available, or may aggregate to form the intracellular granules of hæmosiderin. The latter is probably inert, although it is apparently possible for iron in this form to re-enter the circulation as a result of deliberate iron deprivation.

It seems better to abandon the term 'storage' iron and to consider that iron which is not actively in use for oxidation-reduction systems constitutes a 'labile pool' (Greenberg & Wintrobe 1946). The ferritin molecule has now been visualized by electron microscopy and apparently comprises four constituent iron containing groups linked to protein. Apart from its storage function and the postulated carrier mechanism in mucosal and reticulo-endothelial cells, ferritin has specific physiological powers (Mazur *et al.* 1955). It is a vaso-depressant, inhibiting vasoconstriction, possesses some anti-diuretic action and serves as an intermediary in normal adrenaline metabolism. The studies of Shorr (1955) would suggest that its release in certain forms of surgical shock associated with liver hypoxia is of physiological significance in the body defence mechanisms, but we are still ignorant of how or why this molecule takes part in reactive states.

If one can conceive that iron in ferritin form is able to undertake specific functions and if the presence of a 'labile pool' can be accepted, then it may well be so that ferritin is not a single entity. There may be a constant dynamic interchange of iron to and from the various enzyme systems. For many years it has been a physiological axiom that such systems are 'inviolate' (Hahn & Whipple 1936) and that the natural economy cannot permit interference with or deprivation of such fundamental processes. This may not be true for there is no specific evidence to support such a concept: it has been shown to the contrary in experiments with rats fed iron deficient diets and subsequently bled, that the decline in hæmoglobin is equalled and even exceeded by a drop in the liver cytochrome C concentration (Beutler 1957).

It would perhaps be valid to include all aspects of iron metabolism as subject to a substantial daily turnover: this being most obvious in hæmoglobin because the quantity of iron involved and the relative simplicity of its assessment have long permitted this parameter to be measured with ease. The possibility of a constant interchange of ionic iron to and from enzyme systems, muscle and blood respiratory pigments, and intracellular ferritin, may be relevant to the so-called 'anæmia of infection'. This relatively infrequent phenomenon has not yet been explained. It is shown clinically by an apparent iron deficiency anæmia failing to respond to oral or parenterally administered iron during infection but doing so immediately the infection has been controlled. Although usually benign, this anæmia may assume severe proportions and can lead to exacerbation of the underlying disease.

It is suggested that the body economy is altered in the presence of extreme infection so that iron, following its customary metabolic pathways, is no longer preferentially utilized for the synthesis of hæmoglobin. This may be a direct depressant effect of infection and body reaction. Cartwright & Wintrobe (1952), however, suggest that the switch away from hæmoglobin synthesis results from an increased demand for iron by the tissue iron-dependent enzymes with a diversion of ferritin away from its normal pathways.

It is difficult to believe that alteration in enzyme requirements, which are so slight in comparison to that of hæmoglobin, could be sufficient to alter the *status quo*, yet this might occur if the body were to overcompensate by specifically denying one form of ferritin utilization; it is relevant, in this context, to note that during anæmia of infection the reduced hæmoglobin synthesis is typically associated with a low plasma iron level and a poor response to oral therapy. Yet intravenously administered iron is rapidly cleared from the plasma and, by inference, immediately taken into the ferritin complex, without increasing the hæmoglobin concentration.

Summary

An attempt has been made in this brief survey to stress that iron metabolism is involved in vital systems in addition to that responsible for hæmoglobin synthesis. These may receive some sort of preferential allocation so that any decrease in the circulating level of hæmoglobin can be taken as a direct indication of a parallel decline in supplies of iron for enzyme or co-factor activity.

This is not always the case for, contrary to commonly accepted tenets, the iron-dependent enzymes may become deficient or ineffectual despite a normal hæmoglobin level: this may account for certain ill-defined subjective symptoms displayed by patients, usually women, who are not anæmic yet have a low plasma transferrin level. Their symptoms are readily corrected by the intravenous administration of iron.

Reference is made to the other properties of ferritin, commonly regarded as a storage molecule but probably existing in many forms possessing independent physiological significance.

As iron metabolism in domestic animals appears to be closely similar to that in humans, an analogous situation may obtain. Iron deficiency might exist without tell-tale anæmia, a circumstance of possible relevance in those animals at risk, such as the laying hen or breeding sow, where a considerable iron through-put is inevitable.

REFERENCES

Beutler E (1957) *Amer. J. med. Sci.* **234**, 517
Beutler E & Blaisdell R K
(1958) *J. Lab. clin. Med.* **52**, 694
(1960) *Blood* **15**, 30
Cartwright G E & Wintrobe M M
(1952) Advances in Internal Medicine. Chicago; **5**, 165
Davidson W M (1960) Lectures on Hæmatology. Cambridge; p 18
Dickman S R & Cloutier A A (1950) *Arch. Biochem.* **25**, 229
Greenberg G R & Wintrobe M M (1946) *J. biol. Chem.* **165**, 397
Greig E D W (1898) *J. Physiol.* **22**, 355
Hahn P F & Whipple G H (1936) *Amer. J. med. Sci.* **191**, 24
Henderson I D (1954) *Lancet* i, 493
Indovina I (1951) *Amer. J. Physiol.* **165**, 348
Jennison R F & Ellis H R (1954) *Lancet* ii, 1245
Mazur A, Baez S & Shorr E (1955) *J. biol. Chem.* **213**, 147
Shorr E (1955) Shock and Circulatory Homeostasis. *Jos. Macy Jr Found. Rep.*, p 229
Waldenström J (1946) *Acta med. scand.* suppl. **170**, 252

The following paper was also read:

Transferrins and Iron Transport
Dr D J Perkins (*London*)

Meeting February 16 1961

A laboratory visit was paid to the Royal College of Surgeons of England and the Institute of Basic Medical Sciences, Lincoln's Inn Fields, London.

Meeting June 21 1961

The meeting was held at the Laboratories of the Pharmaceutical Division of Imperial Chemical Industries Ltd, Fulshaw Hall, Wilmslow, Cheshire, by kind invitation of the Directors. Members were conducted round the various departments of the Research Laboratories, including the animal houses, and were shown a film entitled **Breeding Clean Animals**. Mr J E Davison described the work of the laboratory and Dr G E Paget spoke on the film.

Section of Endocrinology

President H L Sheehan MD

Meeting April 26 1961

(continued from September 'Proceedings' p 754)

Short Paper

The Adrenal Medulla, the Adrenal Cortex, Sodium and Blood Pressure [*Abridged*]

by E J Ross MD (*London*)

That the adrenal medulla and the adrenal cortex are in close anatomical contiguity is beyond dispute. Whether there is an equally close functional relationship is the subject of the present discussion.

Attention was directed to this problem by observations on a patient with persistent hypertension due to a phæochromocytoma who developed adrenal insufficiency and, despite the fact that she was still harbouring a functioning phæochromocytoma, became so hypotensive that she could not stand up. This case is reported in full elsewhere (Ross 1961).

It is well recognized that hypotension is a feature of advanced adrenal failure. Several factors, such as sodium loss, decreased circulating plasma volume and so on, may play a role in the reduction of blood pressure. Observations on the patient mentioned above, however, suggest that perhaps the pressor activity of catecholamines is reduced in the absence of adrenal cortical hormones, i.e. adrenal cortical hormones are perhaps permissive, in the sense used by Ingle (1952), for the action of medullary hormones. Alternatively, the relationship between the two may be purely secondary. Various aspects of this relationship will be considered.

(1) The pressor effect of noradrenaline is weakened by adrenalectomy (Ramey *et al.* 1951, and others).

(2) The simultaneous administration of hydrocortisone (Ross 1961) or deoxycorticosterone (Schürgen 1947) does not potentiate the pressor effect of noradrenaline.

(3) The simultaneous administration of aldosterone with noradrenaline potentiates the effect of noradrenaline in low dosage (Table 1).

Table 1

Pressor effect of noradrenaline potentiated by aldosterone in 3 normal subjects (a, b, c)

Dose (μg/kg/min)	0·1	0·2	0·3
Normal subjects	*Increment of blood pressure (mm Hg)*		
(*a*) Without aldosterone	+10/22	+26/36	+52/46
With aldosterone	+24/30	+26/36	+52/44
(*b*) Without aldosterone	+12/22	+48/38	
With aldosterone	+18/28	+42/36	
(*c*) Without aldosterone	+24/18	+70/34	
With aldosterone	+40/30	+74/38	

(4) The pressor effect of noradrenaline is potentiated by the long-term administration of steroids plus sodium chloride (Raab 1942, Ross 1961).

(5) The potentiation of noradrenaline during prolonged steroid therapy is weakened by simultaneous sodium deprivation (Selye *et al.* 1943, and others). Similarly, the development of steroid hypertension is prevented by sodium deprivation (Raab *et al.* 1952).

(6) In normotensive subjects, the systolic response to noradrenaline is weakened by sodium deprivation (Raab *et al.* 1952, Ross 1961) although this has been denied (Dahl 1957). Diuretics also weaken the response to noradrenaline (Merrill *et al.* 1958, and others).

(7) Reduction of plasma volume follows the administration of diuretics or sodium deprivation.

Restoration of plasma volume to normal has been reported to restore pressor response to normal in rats (Dustan & Takagi 1960) and in man (Wanko & Freis 1958). Experiments by the author fail to confirm this (Ross 1961). One must conclude that pressor response to noradrenaline does not solely depend upon circulating vascular volume.

(8) An increased sodium content in muscle and other tissues has been reported in hypertensive animals and patients (reviewed by Tobian 1960). Tobian & Fox (1956) found an increased sodium content in the walls of the femoral arteries of dogs during noradrenaline infusions. A fall in plasma sodium concentration occurs during noradrenaline infusions (Friedman, Friedman & Nakashima 1957, Friedman, Butt & Friedman 1957, Ross 1961). The rise of diastolic pressure during noradrenaline infusions is directly related to the fall of plasma sodium concentration (Ross 1961). The sodium lost from the plasma moves into cells. The concept that the responsiveness of the vascular musculature to noradrenaline is inversely related to the trans-membrane sodium gradient is supported (Friedman *et al.* 1959, Raab 1959).

Conclusions

The functional relation of the two parts of the adrenal gland is indirect, mediated through the sodium ion. The adrenal cortex indirectly modifies the response to noradrenaline in two ways: (1) By its effect on plasma volume resulting from its control of sodium excretion by the renal tubules, and (2) by an effect upon the intracellular distribution of the sodium ion.

As an illustration, the consequence of dietary sodium restriction is reduction of plasma volume, which weakens noradrenaline responsiveness but results also in the increased secretion of aldosterone which potentiates the effect of noradrenaline, perhaps by increasing intracellular sodium content. The net result is the protection of the blood pressure from the results of fluctuation of sodium intake.

REFERENCES

Dahl L K (1957) *Circulation* **15**, 231
Dustan H & Takagi H (1960) *Circulation* **22**, 741
Friedman S M, Butt M & Friedman C L (1957) *Amer. J. Physiol.* **190**, 507
Friedman S M, Friedman C L & Nakashima M (1957) *Circulation Res.* **5**, 261
Friedman S M, Jamieson J D & Friedman C L (1959) *Circulation Res.* **7**, 44
Ingle D J (1952) *J. Endocrin.* **8**, xxiii
Merrill J P, Guinand-Baldo A & Giordano C (1958) *Clin. Res. Proc.* **6**, 230
Raab W (1942) *Amer. Heart J.* **24**, 365
(1959) *Amer. J. Cardiol.* **4**, 752
Raab W, Humphreys R J, Makous N, de Grandpré R & Gigee W (1952) *Circulation* **6**, 373
Ramey E R, Goldstein M S & Levine R (1951) *Amer. J. Physiol.* **165**, 450
Ross E J (1961) *Quart. J. Med.* **30**, 285
Schürgen G (1947) *Klin. Wschr.* **24–25**, 593
Selye H, Hall C E & Rowley E M (1943) *Canad. med. Ass. J.* **49**, 88
Tobian L (1960) *Physiol. Rev.* **40**, 280
Tobian L & Fox A (1956) *J. clin. Invest.* **35**, 297
Wanko A & Freis E D (1958) *Circulation* **18**, 792

Meeting June 28 1961

Paper

The Stein-Leventhal Syndrome [*Abridged*]

by Professor Albert P Netter (*Paris*)

From an analysis of 7 cases Stein & Leventhal (1935) described a syndrome characterized by the following symptoms: Amenorrhœa; hypertrophied, pale, micropolycystic ovaries surrounded by a thick capsule and containing no corpora lutea; hirsutism and obesity; and sometimes, but not always, hypertrophy of the breasts. For treatment they advocated a wedge resection of the ovaries and obtained favourable results.

This description clarified the problem of 'sclerocystic ovaries' which had been the subject of many papers in the older literature. The treatment had been suggested by Kosmak (1913–14) and by Walther (1913). Since then there have been many discussions regarding the causes, diagnosis and pathogenesis of the condition. These, instead of throwing light upon the problem, have tended to aggravate the confusion so that at the First International Congress of Endocrinology (1960), an American delegate said that this syndrome is the 'garbage can' of ovarian endocrinology.

This rather confusing situation arises from the choice of the criteria defining the syndrome. Some authors include in the syndrome all cases of

hirsutism with oligomenorrhœa; others give the name of Stein-Leventhal syndrome to all large cystic dystrophic ovaries regardless of the origin of the condition, which may be infective, psychogenic or congenital; others consider that the sole criterion is an anatomical one making the Stein-Leventhal syndrome synonymous with hyperplasia of the theca interna.

The Criteria

The criteria which we accept for the syndrome are the following:

Oligomenorrhœa: This must be extreme, the menses appearing at most four or five times a year, or possibly only twice. Some of our patients have been young girls suffering from primary amenorrhœa, or young girls who have menstruated only once or twice since the menarche. The oligomenorrhœa must have grown progressively worse. It often happens that soon after the menarche the cycle is not very long, about 45–60 days, then slowly it becomes longer and may last three or four months or even more. Moreover, the oligomenorrhœa is independent of any psychological factor. These patients do not feel the nervous tension noticeable in young girls suffering from acquired polycystic ovarian dystrophy.

Sterility: This is almost always the primary sterility due to the total absence of the formation of corpora lutea. Nevertheless, some patients have had one child or even two because of the occurrence of one or two ovulatory cycles before the age of 22.

Luteal insufficiency: The cause of the sterility is the luteal insufficiency. This diagnosis is made by keeping a basal temperature chart for several months; an assay for pregnanediol performed shortly before menstruation will have negative results; and an endometrial biopsy shows the absence of any secretory pattern.

Hirsutism and obesity: We do not regard these symptoms as being essential elements in the Stein-Leventhal syndrome.

Condition of the ovaries: Physical examination usually reveals enlarged ovaries. They are much harder than normal, and their outlines are smooth without the nodularity of normal ovaries. They are painless, in contrast to the acquired micropolycystic ovaries. Their size remains the same during the menstrual cycle, whereas in infective or psychogenic dystrophy the ovaries become greatly enlarged before menstruation and revert to normal size as soon as menstruation begins.

It is not so much the enlargement of the ovaries as their hardness, smooth contours, painlessness and constant size which are the fundamental elements of the Stein-Leventhal syndrome. On examination by culdoscopy the capsule of these ovaries appears pale, smooth and shining.

Pathology

The Stein-Leventhal ovary is characterized by a thick capsule, which resembles a shining, pale albuginea. It has been claimed that thecal hyperplasia is a major histological finding. The principal criteria are:

The capsule: The capsule surrounding the Stein-Leventhal ovary has a regular and even thickness. In common micropolycystic ovaries some areas have a very thick capsule while in other places cystic follicles bulge right up to the surface of the ovary. In the Stein-Leventhal syndrome on the other hand the cysts are never very large. Their sizes vary in diameter from about 5–8 mm, whereas in common micropolycystic ovaries the cysts vary greatly in size, the bigger ones reaching a diameter of 50 mm or even more.

Histological features: The essential histological features include the lack of corpora albicantia which proves that no corpus luteum has ever been formed; the straight line of primary follicles under the ovarian capsule; hyperplasia of the theca interna, a feature to which some authors give considerable emphasis. Before we started using tests with chorionic gonadotrophin no such hyperplasia was observed but, since we adopted this test as a routine, thecal hyperplasia has been a constant finding, even when there has been a lapse of several months between the test and the operation. The hyperthecosis described in the literature may perhaps have been the result of a previous therapeutic stimulation by gonadotrophic hormone.

Biological Study

The endocrine aspects of the Stein-Leventhal syndrome have been extensively studied. There are no characteristic features. Usually the 17-ketosteroids are normal, and this is a striking finding in the cases where hirsutism is present. Chromatography, however, sometimes reveals that the androsterone is generally higher than the etiocholanolone.

The so-called follicle stimulating hormone is normal or slightly elevated; values between 5–50 mouse units are usually observed. On the other hand, œstrogens are often low. Using the biological method of Henry & Thevenet (1962) we have obtained results varying between 4–12

μg/24h, while normal levels are 8–20 μg in the follicular phase, and 20–40 μg in the luteal phase. Using chemical methods the results obtained are a little higher because œstriol, which is biologically inactive, is in a higher proportion than in normal urine.

The daily urinary excretion of pregnanediol is less than 500 μg; the temperature curve is monophasic and low; biopsy of the endometrium yields either no fragments, or a small fragment which is in the proliferative stage. We have not observed a secretory stage.

The Dynamic Test

We have used a method for a dynamic test consisting first of inhibition of the adrenal cortex by dexamethasone, followed while inhibition was still maintained, by stimulation of the ovaries with chorionic gonadotrophin (HCG). This test is usually completed in twelve days, during which time the patient receives 3 mg dexamethasone daily, and 5,000 units of chorionic gonadotrophin on the sixth, seventh and eighth days. Urine is collected on the day before starting the test, and subsequently on the fifth and twelfth days of the test.

The following assays are performed: 17-ketosteroids by Jayle's method (Jayle *et al.* 1953, Crepy & Jayle 1953); 17-hydroxycorticosteroids by Silber & Porter's method (1954) as adapted by Schöller *et al.* (1957); pregnanediol by Crepy's method (Crepy *et al.* 1956, Jayle *et al.* 1959), this being a variant of Brown's method (Klopper *et al.* 1955); œstrogens by a variant of Brown's method (Brown 1955, Brown *et al.* 1957) separating the œstriol fraction from the whole of the œstrone-œstradiol fraction.

Results: In a normal woman the 17-ketosteroids fall, in five days, to below 2 mg/24h, and the 17-hydroxycorticosteroids to below 1·5 mg. On the fifth day of cortical inhibition the residual rate is on the average 15% of the original rate for 17-ketosteroids, and 20% of the original rate for 17-hydroxycorticosteroids. The administration of chorionic gonadotrophin does not modify the excretion of 17-ketosteroids in a normal woman.

Results in the Stein-Leventhal syndrome: In patients suffering from the Stein-Leventhal syndrome we have noted the following differences from the normal:

On the fifth day the residual rate of 17-ketosteroids remains above 2 mg/24h. The amount of 17-ketosteroids in the urine usually rises after the chorionic gonadotrophin is given despite the fact that the adrenocortical inhibition is maintained with dexamethasone. Furthermore, the 17-ketosteroids are constituted almost entirely of androsterone and etiocholanolone (together they constitute about 90% of the total).

On the other hand, the 17-hydroxycorticoids do not rise. This fact serves as a control proving that the patients have really taken the dexamethasone, and also it supports the extra-adrenal origin of the increased excretion of the 17-ketosteroids after the administration of gonadotrophin.

The fact that the pregnanediol remains low proves the absence of a corpus luteum.

The œstrogens rise considerably. Very often they start rising on the fifth day of the test reaching their peak on the twelfth day.

There is a higher proportion of œstriol relative to the amounts of œstrone and œstradiol in the œstrogens, both before and after the stimulation by gonadotrophin. While the normal proportion of œstriol to œstrone + œstradiol is less than 1·5 : 1 in the Stein-Leventhal syndrome it is often greater than 2 : 1, and sometimes reaches 4 : 1.

Table 1
Responses in Stein-Leventhal syndrome

	17-KS	*A+E*	*17-OHCS*	*F3*	*F1+F2*	*PG*
Before dexamethasone	8·2	5·1	3·3	19	7	0·4
After dexamethasone	3·9	3·2	0·8	28	10	0·4
After dexamethasone +HCG	4·8	4·2	0·4	35	18	0·8

17-KS = 17-ketosteroids mg/24h
A+E = androsterone + etiocholanolone
17-OHCS = 17-hydroxycorticosteroids
F3 = œstriol
F1+F2 = œstrone + œstradiol
PG = Pregnanediol
PT = Pregnantriol
DHA = Dehydro-epi-androsterone

In certain cases a disproportion has been found between androsterone and etiocholanolone, the excretion of the former being sometimes twice that of the latter, which is the reverse of the normal.

Table 1 shows the responses to this test in the Stein-Leventhal syndrome, Table 2 the responses in normal women in the active phase of sexual life, and Table 3 the responses in allied conditions.

Table 2
Responses in normal women in the active phase of sexual life

	17–KS (mg/24h)						
	E+A	*DHA*	*17–OHCS*	*PG*	*PT*	*F3*	*F1+F2*
Before dexamethasone	5·3 (3·0–7·2)	1·0 (0·5–2·0)	5·5 (3·9–7·8)	5·0 (3·5–7·0)	1·5 (1·0–2·0)	25 (15–30)	15 (10–20)
After dexamethasone	1·5 (0·9–2·3)	0·0	0·8 (0·4–1·4)		0·5 (0·2–1·0)		
After dexamethasone +HCG	1·3 (0·9–2·0)	0·0	0·8 (0·4–1·2)	8·0 (6·0–12)	1·5 (1·0–2·0)	50 (30–60)	30 (20–35)

Table 3
Responses in allied conditions

	Premenopausal states				*Luteal insufficiency of hypophyseo-hypothalamic origin in the post-puberal oligomenorrhœas and metrorrhagias*			
	17–KS	*17–OH*	*F1+F2+F3*	*PG*	*17–KS*	*17–OH*	*F1+F2+F3*	*PG*
Before dexamethasone	6·7	2·9	15	0·5	6·3	2·5	11	0·25
After dexamethasone	1·4	0·7	18	0·5	1·1	0·8	15	0·30
After dexamethasone +HCG	1·2	0·4	31	1·5	0·9	0·7	20	0·15
	Luteal defects of hyperadrenocorticism				*Luteal defects of acquired micropolycystic ovarian dystrophy (psychogenic or infective)*			
Before dexamethasone	23	8·3	5	1·2	7·8	3	–	0·2
After dexamethasone	1·8	1·4	20	-	2·3	0·8	–	0·3
After dexamethasone +HCG	1·4	2·5	20	6·8	3	0·5	–	3·5

For abbreviations *see* Table 1

From the comparison of these Tables it can be seen that in normal women, in aluteinism of hypothalamic or adrenal origin or of premenopausal states, there is a striking decrease of urinary 17-ketosteroids during the test. In aluteinism of hyperadrenocorticism, the basal rate of 17-ketosteroid excretion is usually higher than in the Stein-Leventhal syndrome.

It will also be noted that, contrary to what might be expected, the premenopausal ovary can react to intense stimulation by secreting more œstrogens, and even in some instances by producing a corpus luteum. This fact seems to be of general interest in endocrinology. It shows that a gland with an autonomous impairment of secretion can respond to intense stimulation. It is in accordance with some reports of mild Addison's disease reacting to ACTH. Conversely we have obtained no response to gonadotrophin in our cases of ovarian insufficiency of hypophyseo-hypothalamic origin.

In the acquired syndrome of micropolycystic ovaries (the most common form of which occurs after abortion and has probably an acquired ætiology, both infective and psychogenic) the dynamic test gives a response which statistically is half-way between the Stein-Leventhal and the normal. There is an overlap between the two diseases, so that the test cannot be considered as specifically diagnostic of the Stein-Leventhal syndrome.

The adreno-ovarian system may respond in the same way in patients with masculinizing tumours of the ovary and in some women who are apparently normal as it does in the Stein-Leventhal syndrome. In one case of mammary atrophy with regular luteal cycles, the dynamic test showed a lack of inhibition of the 17-ketosteroid excretion by dexamethasone.

The dynamic test as we have described it is

helpful in the diagnosis of the Stein-Leventhal syndrome, but it is no more characteristic than any other of the clinical symptoms or the histological pattern of the ovary.

Chromosomal Study (very much abridged)
Three cases[1] were studied:

One on the borderline between ovarian agenesis and Stein-Leventhal syndrome showed a deletion of the major part of the long arm of one chromosome, identical to Patricia Jacob's case.

Two were typical cases of Stein-Leventhal syndrome as we defined it: In the first we found a mosaic of 46 normal chromosomes and of 47 chromosomes, including 3 X (triplo X). In the second we found a mosaic of 46 normal chromosomes and of 46 chromosomes, one of the X having undergone the same deletion as in the case above mentioned.

The author discusses the relations between the chromosomal defect and the enzymic defect of the syndrome.

In certain cases with marked hirsutism, chorionic gonadotrophin induces an increase of urinary pregnantriol, which seems to result from an enzymic block of the synthesis of the œstrogens, probably related to the chromosomal defect.

[1]The details of the reports will be published in the *Annales d'Endocrinologie.*

REFERENCES
Brown J B (1955) *Biochem. J.* **60**, 185
Brown J B, Bulbrook R D & Greenwood F C (1957–58) *J. Endocrin.* **16**, 41
Crepy O & Jayle M F (1953) *Ann. Biol. clin.* **11**, 233
Crepy O, Meslin F & Jayle M F (1956) *Bull. Soc. Chim. biol., Paris* **38**, 505
Henry R & Thevenet M (1962) Dosage biologique des œstrogènes urinaires (to be published)
I International Congress of Endocrinology, Copenhagen, July 1960 (1960) *Acta endocr., Copenhagen* Suppl. Nos. 50 & 51
Jayle M F, Baulieu E E & Gonzales F (1953) *Ann. Endocr., Paris* **14**, 642
Jayle M F, Judas O & Crepy O (1959) *Bull. Soc. Chim. biol., Paris* **41**, 1441
Klopper A, Michie E A & Brown J B (1955) *J. Endocrin.* **12**, 209
Kosmak G W (1913–14) *Bull. Lying-in Hosp. N. Y.* **9**, 107
Schöller R, Busigny M & Jayle M F (1957) *Path. Biol. (Sem. Hôp. Paris) Arch. Biol. méd.*, Fiche tech. No. 2 March 1957, p 49
Silber R H & Porter C C (1954) *J. biol. Chem.* **210**, 923
Stein I F & Leventhal M L (1935) *Amer. J. Obstet. Gynec.* **29**, 181
Walther C (1913) Résultats éloignés des opérations conservatrices des Ovaires. Académie de Médecine, séance du 18 Mars 1913. *In:* Titres et Travaux Scientifiques de C Walther, Addendum. pp 34–35

Section of Pædiatrics

President B E Schlesinger OBE FRCP

Meeting June 10 1961
at the Children's Hospital Sheffield

Short Papers [*Abridged*]

The Changing Pattern of Pædiatrics in a Children's Hospital 1876–1961

by Professor R S Illingworth MD FRCP (*Sheffield*)

The Children's Hospital, Sheffield, was established in Brookhill in 1876, with 8 beds and an income in the first year of £153. It was moved to the present site in Western Bank in 1881, with 16 beds. An East End Branch for out-patients only was opened in 1892 and maintained till 1931. The present establishment of the Children's Hospital is 206 beds. From the beginning the out-patient practice was a large one, and the total number of new out-patients and new casualties seen in it up to the present date has been about 835,000. In 1882 the annual report stated that the total of 3,271 new out-patients with 14,230 attendances 'equals the numbers attending the two largest Metropolitan Children's Hospitals, *viz.* the Hospital for Sick Children, Great Ormond Street, and the Victoria Hospital, Chelsea'.

The dependence on voluntary contributions was constantly reflected by comments in the Annual Reports. For instance, in 1879 it was noted that 4 of the 12 beds remained unused throughout the year for want of funds. In 1903 the report stated 'There is always something in an institution like ours, and without asking, we would like to mention the fact that a glass instrument cabinet would be much appreciated in our operating theatre'.

The shortage of nurses was referred to in the report of 1886 which stated: 'During the last year there have been several very serious cases requiring a special nurse, and the subscribers can well understand that out of a working staff of two nurses, one day and one night, this is a matter very difficult of accomplishment, and it has only been by the matron leaving her other duties and acting as nurse herself, that it has been possible to get the work done.'

There are interesting notes about the hospital diet in old annual reports. In 1877 the staff wrote as follows: 'If the mother has plenty of milk, let her give the child nothing else. Three out of 4 children brought up by the hand die.' 'At 10 months the child should have thin broth of beef tea every day. No child under 2 years old ought to eat at your table.'

Out-patient consultations: The old annual reports provide interesting analyses of the work done by the hospital, including analyses of out-patient consultations, in-patient operations and casualties. A selection of figures concerning out-patient consultations are given in Tables 1 and 2.

Table 1
1877: New out-patients, total 3,934

		Total	*Percentage*
Measles	190		
Scarlet fever	193	663	16·8
Whooping cough	280		
Bronchitis		571	14·5
Diarrhœa		548	13·8
Improper feeding		316	8·0
Worms		115	2·9
Dyspepsia		140	3·6
Stomatitis		96	2·4
Phthisis		50	1·3
Rickets		27	0·7

Table 2
1910: New out-patients, total 12,548

	Total	*Percentage*
Debility, malnutrition, athrepsia	978	7·8
Diarrhœa	832	6·6
Bronchitis	771	6·1
Eczema	571	4·5
Impetigo	570	4·5
Rickets	425	3·4
Worms	411	3·3
Tinea	300	2·4
Anæmia	272	2·2
Conjunctivitis (including gonorrhœa 16, tuberculosis 15)	261	2·1
Rheumatic fever and chorea	234	1·8

The high incidence of infectious diseases in 1877, of diarrhœa, improper feeding, malnutrition, rickets, eczema, and rheumatic fever, will be noted.

Table 3
Changing pattern of medical conditions

Diarrhœa	*Year*	*Percentage of new outpatients*
	1877	13·8
	1900	9·8
	1910	6·6
	1947	1·1
	1960	0·05
Worms	*Year*	*New out-patients total*
	1877	115
	1900	116
	1910	411
	1947	97
	1959–60	0
Syphilis	*Year*	*New out-patients total*
	1883	90
	1900	41
	1910	43
	1920	92
	1924	130
	1947	5
	1959–60	0
Tuberculosis	*Year*	*Percentage of all admissions (excluding isolated positive tuberculin reaction)*
	1909	44·8
	1947	4·7
	1948	4·6
	1959	0·13
	1960	0·10
Tuberculous meningitis	*Year*	*Admissions total*
	1950	35
	1960	2
Tuberculosis	*Year*	*New out-patients total*
	1948	93
	1959	5
	1960	3
Rheumatic fever and chorea	*Year*	*New out-patients total*
	1910	234
	1947	66
	1948	137
	1959	5
	1960	1

	1948	*1959*	*1960*
Nephritis			
In-patients	60	42	21
New out-patients	38	12	2

Rickets	*Year*	*New out-patients total*
	1900	243
	1910	425
	1947–8	17
	1960	0
Pink disease	*Year*	*New out-patients total*
	1948	57
	1959–60	0

	1947	*1948*	*1959*	*1960*
Lung collapse				
In-patients	109	85	45	28
Percentage of total in-patients	3·7	2·9	0·8	0·5
New out-patients	66	85	4	3
Bronchiectasis	74	52	11	6

	1947–8	*1959–60*
Non-tuberculous pleural effusion or empyema	58	7

Table 4
Decreasing death-rate (percentage of all admissions)

Year	1900	1910	1920	1930	1940	1950	1960
Deaths (%)	11·5	9·2	10·0	10·8	8·6	2·5	2·1

Table 5
Changing pattern of surgical conditions

Operations	*Year*	*Total operations*
	1880	27
	1890	196
	1900	234
	1910	264
	1920	465
	1930	456
	1940	630
	1950	1,363
	1960	3,731

Surgery in the first month of life	
1948	29
1960	193

Appendicectomy	*Year*	*Total*	*Percentage of operations*
	1877–1902	0	0
	1903	1	0·4
	1910	4	1·5
	1947	56	6·1
	1948	98	9·2
	1959	225	7·2
	1960	242	6·5
Intussusception	1877–1896	0	
	1897	1	
	1898–1903	0	
	1910	8	
	1947	33	
	1960	54 (including barium reduction)	
Hernia operations	1877–1897	0	
	1898	1	
	1899	20	
	1910	46	
	1947	85	
	1960	282	
Harelip operations	1878	2	
	1947	33	
	1948	42	
	1959	65	
	1960	114	
Antrum washouts	1948	0	
	1960	255	
Strabismus operations	1947	36	
	1948	72	
	1960	158	
Hydrocephalus or meningomyelocele operations	1947	15	
	1959	133	
	1960	175	

Table 6
Poisoning

	Year	*Total*
In-patients	1947–1948	12
	1959–1960	118
Poisonings treated in casualty department	1877–1902	0
	1903	1
	1903–1914	Average 4 per year
	1960	74

Decreased incidence of certain diseases: The figures in Table 3 show striking reductions in the incidence of various diseases, and Table 4 illustrates the decreasing death-rate.

Increasing role of surgery: The striking increases in the surgical work of the hospital are shown in Table 5.

The old reports throw interesting light on to the nature of surgical procedures. For instance, in 1888, 57 of a total of 170 operations were for the treatment of osteitis. In 1900 there were 19 operations for arthrotomy of ankle, knee, elbow or wrist. In 1912 there were 14 operations for excision of joints (presumably tuberculous).

Poisoning: No child was admitted to the hospital on account of poisoning until 1919. Table 6 gives relevant figures.

Increasing pressure of work: Table 7 indicates the increasing pressure of work.

Table 7
Increasing pressure of work

Year	Total No. of beds	Admissions	New casualties	New out-patients
1940	157	2,068	1,014	?
1950	208	3,341	5,862	6,129
1960	205	5,780	7,878	8,101

	Admissions under 1 year of age	X-ray films taken	Total No. of operations
1940	583	2,247	630
1950	484	15,101	1,363
1960	1,266	14,400	3,731

Duration of stay: In 1880 only 9% of cases admitted stayed less than seven days; in 1890 the figure was 11% and in 1959 and 1960 it was 62%.

The average duration of stay in hospital in 1890 was 44·5 days; in 1940 it was 22·6, in 1950 18·2, and in 1960 eleven days.

Cost of drugs: The cost of drugs in 1877 was £3 10s 0d; in 1900 it was £116 9s 0d and in 1920 £396 2s 10d. By 1940 it had risen to £1,417 0s 9d. The increase since then has been enormous.

This increase occurred in spite of a change in policy in the out-patient department at the beginning of 1947, when an effort was made to reduce out-patient prescribing. In the four years 1943 to 1946 the total number of out-patient prescriptions was 272,665. In the four years 1947 to 1950 the total number was 83,612. This represented a reduction of 189,053 prescriptions.

The cost of an in-patient per week was £2 5s 0d in 1930, £7 2s 11d in 1946 and £34 3s 2d in 1960. In 1890 the cost of sending a patient to a convalescent home was 5 shillings per week.

Visiting: The annual reports in the years following 1930 noted that no visiting would be permitted for the first month of a child's stay in hospital unless he were gravely ill. In 1960 visiting was allowed throughout the day for all patients.

Patients from outside Sheffield: In 1909 there were 60 admissions from outside Sheffield (11·8% of all admissions), all from the immediate vicinity. In 1961, of 1,318 admissions (February to April) 469 came from outside Sheffield (35·6%), many from a very wide area and from a long distance.

The Treatment of Hypospadias

by B S Crawford MB FRCS (*Sheffield*)

The problems encountered in the treatment of hypospadias have been the despair of generations of surgeons. They are enumerated in Table 1 and contrast with the much shorter list of conditions which help towards a successful outcome.

Table 1
Favourable and unfavourable factors

For	*Against*
(1) Good blood supply	(1) Thin skin which tears easily
(2) Scars rarely contract	(2) Presence of urine under pressure
	(3) Post-operative erections
	(4) Post-operative œdema
	(5) Clot retention
	(6) Infection due to moisture and proximity to anus
	(7) Profuse nerve supply
	(8) Anxious parents

In order to repair the defect the available skin has to be advanced to the front of the penis and used not only to cover the raw area created when the penis is straightened, but to provide both lining and cover in the more complicated procedure of urethral repair. Thirty years ago Howard (1932) considered that the more serious forms were probably better left alone, but the application of the buried strip principle by Browne (1949) changed the outlook completely so that cases which were not suitable for treatment by the Ombrédanne (1932) method could be operated on with a good prospect of success. Excellent results have followed the Browne operation (Johanson 1953), but some workers have been dissatisfied with the method (Creevy 1958), largely because of the high fistula rate.

Conolly (1954) reported 121 cases with excellent results although a number of complications were mentioned – e.g. fistula, secondary hæmorrhage, abscess formation, meatal stenosis and trouble with the catheter – which are familiar to those who have treated cases of hypospadias.

Urethral fistula is due to failure to achieve first-intention healing of the covering flaps. In most branches of surgery a slight delay in wound healing may not be important, but in hypospadias it results in failure. If the wound opens slightly for any reason, the growing epithelium is unable to bridge the gap, and as the lining epithelium and skin are so close together, they rapidly join with the inevitable formation of a fistula. *I believe that the leakage of urine is a result of the failure of the flaps to heal rather than the cause of it. Healing is not prevented by the presence of urine – it continues to occur but not in the way the surgeon intended.* Clearly, the known causes of delayed healing such as infection, tension, hæmatoma formation, the use of irritant suture material and scarred flaps must be avoided. It is not always realized that the last cause is important in that certain methods of straightening the penis cause scarring of the ventral skin elsewhere than in the mid-line. These scars reduce the blood supply and therefore the healing powers of the covering flaps.

Most authorities believe that urine is an important cause of fistula, and Browne (1949) states that in its presence true primary union does not occur. This view does not take into account the work of Ombrédanne (1932) whose method is still used with great success. I wish to challenge the accepted view by presenting a series of cases of hypospadias in which there has been no diversion of urine and no apparent ill effect.

Correction of chordee: The Browne (1960) method has been used but the following additions have been made: (*a*) The terminal urethra is freed and retreated by the V-Y method. (*b*) The dorsal skin is advanced to the front of the penis as the ventral defect is closed. (*c*) The dorsal skin incision is made as usual, but the subcutaneous smooth muscle fibres and veins are freely divided in order to release the skin. In addition a complete dorsal slit is made to allow the prepuce to advance and the large dorsal defect is covered as far as possible by everting the lining layer of the prepuce. Any remaining raw area is covered by a razor graft of non-hair-bearing skin. Covering the defect in this way reduces scarring and infection and prevents the return of the skin to the dorsum during healing. (*d*) The prepucial skin tends to retreat down the penis as the organ is straightened so that it will be impossible to make the urethra reach the end of the penis at the next stage unless the glans is tunnelled. To avoid this, two areas on the glans on either side of what will be the roof of the terminal urethra are 'shaved' (as in the Browne stage II operation), and sutured to adjacent areas of the prepuce which are denuded of skin.

These modifications anticipate the needs of the surgeon at the next operation, particular care being taken to provide a generous amount of skin anteriorly.

Urethral reconstruction: The buried strip of hairless skin is outlined (Browne 1949), but in the method about to be described it is carried on to the prepuce as far as the end of the penis, leaving narrow strips of prepuce attached to the glans. The covering flaps are raised in the usual way by wide undermining. The dorsal relaxation incision is freely made, the details depending upon the type of case and previous treatment. If the penis has not been operated on before, the incision is the same as that described in the straightening operation, but in perineal cases it should be extended a short distance in a 'swallow-tail' fashion on either side of the root of the penis. When the dorsum has been grafted previously the scars at each side of the graft are incised and opened out until the flaps are loose.

The covering flaps are now united in the mid-line using a double layer of fine stainless steel wire sutures. The first layer picks up the subcutaneous tissue 2–3 mm from the free edge and the second unites the free edges of the skin and covers the first. The 'bites' are close together and the wires must be kept running freely in order to make their removal easy.

Hæmostasis must be perfect, otherwise clot retention may occur. Finally, saline from a dental chip syringe is injected along the urethra to make sure no leakage occurs.

Largely on the grounds that severe dysuria would occur, Browne (1960) objected strongly to Mustarde's (1955) suggestion that urinary diversion might be avoided. I have not found dysuria to be a problem if the flaps are relaxed so that there is little resistance to the passage of urine. Some boys have no pain at all, most of them have some pain only on the first occasion on which urine is passed. Four hours post-operatively a dose of dihydrocodeine 0·75 mg/kg is given, and an hour later the boy is allowed to get up to pass urine. If the bladder is allowed to become distended, emptying will certainly be painful. If this occurs the child should be placed in a warm bath when micturition will readily occur. These children soon cease to require nursing care until the tenth day when the wires are divided close to the skin posteriorly and slipped out.

Mays (1961) writes 'complications are anticipated in every case, and in some measure this prognostication is nearly always realized. It should be clearly understood that a primary uncomplicated result is a desired but seldom accomplished goal'. Having repaired 25 consecutive cases without the occurrence of a fistula I believe that I can disagree with this statement. These results also question the accepted view that urine must be diverted before urethral surgery can be carried out.

This method is not advocated as an alternative to the Browne operation for those who have found his operation unsatisfactory, as it is more difficult to perform. Some surgeons may find the modifications of the straightening operation of value, particularly in cases with marked curvature, but I hope that others will be stimulated to take an interest in a fascinating problem.

REFERENCES
Browne D
(1949) *Post-grad. med. J.* **25**, 367
(1960) *Trans. Int. Soc. Plast. Surg.* 2nd Congr. p 370
Conolly N K (1954) *Brit. J. Surg.* **41**, 615
Creevy C D (1958) *Urol. Survey* **8**, 24, 44
Howard R (1932) In: A System of Surgery. Ed. C C Choyce. 3rd ed. London; **2**, 914
Johanson B (1953) *Acta chir. scand.* suppl. 176, p 17
Mays H B (1961) *J. Urol.* **85**, 55
Mustarde J C (1955) *Brit. J. Plast. Surg.* **7**, 166
Ombrédanne L (1932) Précis Clinique et Opératoire de Chirurgie Infantile. 3rd ed. Paris; p 645

Rh Antibody Titres and Fœtal Wastage

by R R Gordon MC MD MRCP (*Sheffield*)

The exact place for induction of labour in the management of rhesus incompatibility is not yet clear. It has been suggested (Kelsall *et al.* 1958, Tovey & Valaes 1959) that Coombs antibody titres are a reliable index of whether the fœtus is affected or not and that a high titre will even indicate that it is so severely affected that induction is indicated.

Some serologists, however, do not accept that the Coombs titre is sufficiently accurate technically for it to be used in this way and hitherto no form of Rh antibody titre has been used routinely in the Sheffield Region. It was, therefore, decided to find out whether titres, as performed by the Sheffield Regional Blood Transfusion Service (Drs C C Bowley and Ian Dunsford), were related to the severity of the disease in the infant. This investigation was undertaken in three regional hospitals and the Rh-negative mothers with antibodies were all asked to attend regularly throughout pregnancy. Only the maximum antenatal titre is, however, used in this communication.

In some seventeen months, 160 Rh-incompatible pregnancies have been studied. Induction of labour was undertaken by the obstetricians responsible for the mothers but this was always based on clinical judgment only: the antibody titres were unknown to them. In general, induction was undertaken at term in nearly all patients who had not gone into labour by then; and at 36–37 weeks where there had been a previous stillbirth or severely affected baby and the husband was homozygous for D.

In these 160 Rh-incompatible pregnancies there was a total fœtal wastage of 11·3%. This compares with the 12·8% of Kelsall *et al.* (1958) when induction was based on antibody titres alone and the 12·2% of Tovey & Valaes (1959) in which induction based on antibody titres was used in 'some cases'. Without any induction at all Walker & Murray (1954) had a total fœtal wastage of 14% for the years 1952–53.

In the present series, however, it was certainly possible to confirm that high Coombs antibody titres (1/40 or more) were associated with low cord hæmoglobins, need for exchange transfusion and a high fœtal wastage. In spite of this we do not yet feel that induction of labour based on antibody titres *alone* is justifiable and if they are valuable at all in determining which cases should be induced then it should be possible by combining clinical and serological information to produce a total fœtal wastage well below 10%.

REFERENCES
Kelsall G A, Vos G H & Kirk R L (1958) *Brit. med. J.* ii, 468
Tovey G H & Valaes T (1959) *Lancet* ii, 521
Walker W & Murray S (1954) *Brit. med. J.* ii, 126

Birth Order in Epileptic Children

by T Colver MD and D F Kerridge BSC (*Sheffield*)

A knowledge of birth order can contribute to the evaluation of hereditary and environmental factors in disease. Many clinicians (notably Brain 1926, Bridge 1949, Alström 1950 and Lennox 1959) have explored this matter in epilepsy but without agreeing whether a characteristic pattern exists. It is doubtful, however, if the results of these writers are comparable, since their selections of clinical material were different. The question was therefore re-examined, attention being confined to epileptic children which were either firstborn with a secondborn sib control, or secondborn with a firstborn sib control. Three hundred and forty-eight such sib pairs were collected. To exclude examples of simple fever convulsions, those pairs were excluded in which the reference patient had suffered fewer than ten convulsion days (a convulsion day being defined as any day in which the patient suffered 1 or more convulsions). 'Common life observation periods' were then assigned for each remaining pair with the exclusion of those pairs in which neither sib suffered ten convulsion days during such period. There remained 174 pairs, the firstborn/secondborn ratio among these being 106/68, a difference significant at the 1 in 100 level. Among 84 patients whose symptoms had begun under 2 years of age the firstborn/secondborn ratio was 56/28, a difference significant at the 1 in 200 level. It was concluded that epilepsy, as defined, was more fre-

quent in firstborn than in secondborn children. The problem of the significance of this difference is complex and beyond the scope of the enquiry. The results, however, taken with the similar birth-order differences among stillbirths and first-week deaths are at least consistent with the hypothesis that these occurrences and epilepsy in childhood may have important causes in common.

(A full account of this paper will be published in the *Journal of Neurology, Neurosurgery and Psychiatry*.)

REFERENCES
Alström C H (1950) *Acta psychiat., Kbh.* Suppl. 63
Brain W R (1926) *Quart. J. Med.* **19**, 299
Bridge E N
(1949) Epilepsy and Convulsive Disorders in Childhood. New York
Lennox W G (1960) In: Textbook on Medicine. 10th ed. Eds. R L Cecil & R F Loeb. New York; p 1426

The Mechanism of Deformity in Cerebral Palsy

by W J W Sharrard MD FRCS (*Sheffield*)

The management of the locomotor defects in cerebral palsy is concerned with two objects, to obtain the best functional use of the limbs and to prevent or correct deformity. In the treatment of potential or established deformity, several types of surgical procedure are available and have been used during the past fifty years, including among them tenotomy, neurectomy, tendon transplantation, osteotomy and arthrodesis. Though a good proportion of these operations have been successful, there are some failures and, in a few instances, the final result has been to make the patient's condition worse. Because of this, the use of surgery has been limited in some centres, with the equally disastrous result that deformities not amenable to physical treatment, such as dislocation of the hip or rocker foot, have developed.

Surgical and physical treatment each have their place in the management of deformity in cerebral palsy but the proper contribution that each can make can only be determined through an understanding of the mechanism by which deformities develop. An analysis of the development of deformity and of the results of conservative or surgical treatment in more than 300 patients has shown that the prognosis for the development of deformity and for the likely results of operative treatment can be fairly consistently made.

Neurological teaching has always overemphasized the spastic condition of the limb muscles in the upper motor neuron lesion. It is not sufficiently appreciated that, in almost every case, there is weakness of some muscle groups, amounting in many instances to a complete flaccid paralysis. The muscle groups usually affected by this paralysis are the dorsiflexors of the ankle, extensors of the knee, abductors and extensors of the hip, extensors of the wrist and digits, extensors of the elbow and abductors of the shoulder. Their antagonists usually show normal power and often spasticity as well. The deformities of equinus, knee flexion, hip adduction and flexion leading to dislocation, wrist flexion, elbow flexion and shoulder adduction arise because of the imbalance of muscle power rather than because of spasticity in the deforming muscle groups. If, in the examination of the patient, the spasticity is ignored and attention paid to the relative strength of the opposing muscle groups, whether spastic or not, an almost certain indication can be obtained of the liability to develop deformity.

It has been suggested that weakness in the non-spastic muscle groups arises from the inhibitory effect of spasm in the opposing muscles. Though this may be an additional factor in some cases, it is, in general, unimportant. If the spastic muscles are temporarily paralysed by infiltration of their nerve supply with local anæsthetic, the paralysis in the opposing muscle groups still persists and this is also true following the more permanent effects of neurectomy. Virtually every case in which deformity has subsequently developed has been shown to have partial or complete paralysis of the corresponding muscle group. Conversely, patients in whom no deformity has developed in spite of the presence of considerable spasticity are those in whom paralysis has been slight. Two patients in whom calcaneus deformity had developed following elongation of the tendo achillis were found to have had normal dorsiflexor power before operation even though the calf muscles were very spastic.

Following estimation of the paralysis, which is sometimes difficult and may need to be repeated on several occasions, physical and surgical treatment can be planned with the object of obtaining and maintaining a balance of muscle power in the affected joint using the techniques of tenotomy, tendon transplantation or neurectomy. Since this approach has been employed during the past four years, the result that was anticipated from surgery has been achieved on every occasion save in two patients, and in these the failure was a technical one.

Development of the Mucous Glands in the Trachea

by John L Emery MD DCH
and Avinash Mithal MB (*Sheffield*)

The human lung grows considerably after birth and there are possibly 1,000 times as many alveoli

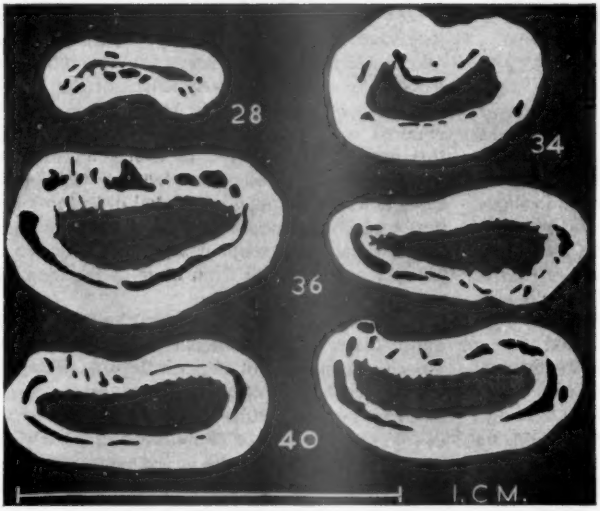


Fig 1 *Photographs of tracings of transverse sections of the trachea from children of different gestation age. Numbers indicate the weeks of gestation of the individual cases. Black areas are mucous glands; white area represents connective tissue and cartilage*

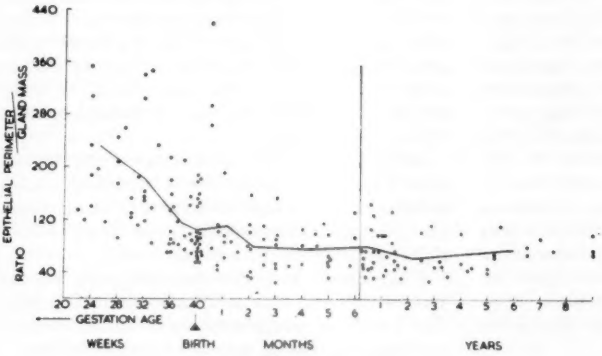


Fig 2 *Showing ratio of the epithelial perimeter of the trachea to the gland mass at different gestation ages and different ages after birth. Each point represents a different case. The solid line is the mean*

in the fully grown person as in the newborn child (Emery & Mithal 1960). That infantile disease and premature birth can influence and be associated with defective proliferation of alveoli has also been demonstrated. There is great individual variation in the microscopic structure of the respiratory tract tissue even from different children of the same age. This is illustrated by part of a study that we have been carrying out on the development of the mucous glands of the trachea.

Projection tracings and weighed cut-outs were done on sections across the trachea, taken 1 cm below the thyroid cartilage from 186 children whose ages varied from 24 weeks gestation to 9 years. Sample tracings showing both the variability in location and quantity of mucous glands are seen in Fig 1.

The amount of gland tissue is related to its functional counterpart, the internal perimeter of the trachea, in Fig 2. The normal range of over 200% is seen in the premature baby. There is a relatively large amount of gland tissue and less variation in the older child. The ratio apparently stabilizes in early childhood and then remains constant.

Clinical variation in the mucus production has been studied very little (Reid 1960) but is of much clinical importance (Laroche 1932). From our findings it is not surprising that some infants produce more mucus than others. The importance of changes in the mucous glands in diseases of children has yet to be investigated.

REFERENCES
Emery J L & Mithal A (1960) *Arch. Dis. Childh.* **35, 544**
Laroche R (1932) *Pr. méd.* **34, 650**
Reid L (1960) *Thorax* **15, 132**

Histochemical Studies on the Catarrhal Rhinitis of Children

by Miles Taylor MD (*London*)

Catarrhal rhinitis of children is a chronic condition which is characterized by a mucopurulent nasal discharge that persists despite all treatment. Histologically the nasal respiratory mucosa shows an increase in the number of mucus-secreting glands, a thickening of the basement membrane and a gradual increase in the amount of fibrous tissue in the subepithelial layers. These changes have been considered previously to be non-specific reactions to infection associated with a reduction in the nasal airway. Histochemical studies, however, indicate that these changes may be due to a metabolic change in the mucosa and this view is supported by clinical observations on the natural history of the disease.

Unlike normal nasal respiratory epithelium, the epithelium in catarrhal rhinitis contains large amounts of the enzyme succinic dehydrogenase. This enzyme indicates the sites of increased metabolic activity which is probably associated with the increase in numbers of the goblet cells in the epithelium. These goblet cells synthesize their sulphated mucins from components that migrate through the basement membrane; and as these components are PAS-positive, this may account for the marked PAS-positive reaction of the basement membrane in this condition. Infected epithelia in other sites show no evidence of increased succinic dehydrogenase activity. It may well be, therefore, that the catarrhal rhinitis of children is a histopathological entity and this hypothesis is strengthened by the observation that the majority of cases cure themselves spontaneously at puberty.

Ætiology of Intussusception

by R B Zachary FRCS and
C W Potter BSC (*Sheffield*)

In the course of eleven years more than 300 children were admitted to the Sheffield Children's Hospital for the treatment of intussusception. During the same period 35 cases were admitted to the Children's Hospital in Seattle, Washington, U.S.A., a city of comparable size. After making allowances for the differing areas of population served by the two hospitals and the numbers of cases admitted to other hospitals in the two cities, it is impossible to escape the conclusion that intussusception is many times more common among the Sheffield children than among those of Seattle.

One line of investigation of this contrast in incidence has been the study of infection by adenovirus in cases of intussusception and in controls. A report on the early stages of this study was made by Ross & Potter (1961). Twenty-four children with intussusception were admitted to this hospital in a period of twelve months. A mesenteric lymph node was taken for study in 21 cases and adenovirus was isolated in 9; for comparison 15 lymph nodes were taken from children of a similar age group at laparotomy or from autopsy material, but from none of these could virus be isolated.

Adenovirus was obtained from the fæces in 15 out of 24 cases of intussusception, compared with 1 positive result out of 41 controls. Throat swabs from 11 out of the 24 children with intussusception gave positive results for isolation of the virus, compared with 1 out of 20 children admitted with a respiratory infection who served as controls.

Serum was taken from the patients on admission (acute serum) and also two to three weeks later (convalescent serum). In order to compare the frequency of neutralizing antibody in the acute serum, 100 sera were taken from normal children between the ages of 3 and 30 months. Between the ages of 7 and 9 months neutralizing antibody to *either* type I or type II was detectable in 50%; by the age of 30 months antibody to *both* types I and II was present in 50%.

In the age group 7 to 18 months antibody to *both* types I and II was found in just over 30%, whereas none of the 24 sera from cases of intussusception (average 13·5 months) had antibody to *both* types I and II at the time of admission.

Complement-fixation tests were done on the acute serum and convalescent serum in 14 out of the 15 cases of intussusception in which the virus was isolated. (Paired sera were not available in 1 case.) In each of the 14 cases there was a fourfold rise in titre. In the 9 cases in which no virus was isolated, adenovirus type II antigen was used, and in none was there a significant (fourfold) rise in titre.

We think that a significant relationship between adenovirus infection and intussusception has been established. Whether it is a causal relationship has yet to be proved.

REFERENCE

Ross J G & Potter C W (1961) *Lancet* i, 81

The following paper was also read:

The Elimination of Tuberculosis in Sheffield Children

J Lorber MD MRCP

Cases were also shown.

Section of Dermatology

President Hugh Gordon MC FRCP

Meeting April 20 1961

Cases

Granuloma of the Groins and Perineum Secondary to Chronic Proctocolitis
O L S Scott MRCP

A C, female, aged 72.
History: This woman has had multiple sinuses of the groin since 1953. She then had deep fissures in the genito-crural regions with sinuses which were believed to be associated with diverticulitis. She did not have ulcerative colitis. A biopsy taken at laparotomy showed non-specific granulation tissue. Colostomy was performed and she gradually improved until she reached the present stage, with fissures, sinuses and epithelial hyperplasia. Dr R E Bowers has drawn my attention to an article by Nevin (1961) on chronic granuloma, in which he particularly stresses Crohn's disease and ulcerative colitis as being the main causes of this condition. It seems to be very difficult to clear up. My patient has had this granulomatous tumour and some people seem to think it would be better to have it excised. I would prefer to leave it alone. This picture does arise in ulcerative colitis but is not stressed in the literature. I believe this patient is probably suffering from Crohn's disease.

REFERENCE Nevin R W (1961) *Proc. R. Soc. Med.* 54, 137

Dr R E Bowers: I have watched a similar patient since 1954. Two or three months ago a stricture was discovered 4 in. within the rectum and this had to be dilated. Biopsy showed chronic pyogenic granulation only.

She was treated with tyrothricin lotion and hydrocortisone locally and ferrous sulphate and vitamin C by mouth. Her anæmia was corrected by blood transfusion. On this therapy she slowly improved and repeat sigmoidoscopy two months later showed a normal mucosa with no ulceration. She was discharged, but was readmitted in January 1961 as her condition had relapsed.
On examination at this time the fissures extended from the natal cleft posteriorly round into the groins anteriorly. They were surrounded by rolled, everted edges, and the possibility of a malignant change was considered. Biopsy, however, again showed only chronic pyogenic granulation tissue. Swabs from the lesions showed a mixed pathology, *B. proteus* and *Bact. coli* being the predominating organisms. No *Myco. tuberculosis* was found. Sigmoidoscopy to 16 cm showed a gross proctocolitis with an œdematous mucosa but no ulceration. Local therapy, as before, was tried, but with little improvement. The treatment was changed to Phenoxetol locally, with daily hydrocortisone retention enemata, which resulted in dramatic improvement.

June 1961: The fissures have lost their rolled, everted edges and the base is much more nearly flush with the skin surface; they have not yet begun to re-epithelialize.

Granuloma of the Groins and Perineum Secondary to Chronic Proctocolitis
C J Hunter-Craig MB (for E J Moynahan FRCP)

E M, female, aged 72.
History: Admitted August 1960, complaining of 'cracking' around the genital area which had been present intermittently since 1952. The present episode started in September 1959, when she felt 'something coming down from the back passage'.
On examination: Rectal prolapse with deep fissuring round the anus, genital area and groins. Hb 57% (8·9 g%). Sigmoidoscopy showed a granular, pus-flecked mucosa, which bled easily.

The following cases were also shown:

Toxic Epidermal Necrolysis – Associated with Butazolidine Therapy Dr J Overton
Cutaneous Leishmaniasis Dr R D Sweet
Oral and Anal Ulceration Treated by Hypnosis Dr B G Gradwell (for Dr J Franklin)
Three Cases treated by Hypnosis: (1) Keratoderma of Feet: Hyperkeratoses of Hands (2) Neurodermatitis of Feet (Two Cases) Dr M J Fenton
Spherocytosis and Chronic Leg Ulceration Dr L Forman and Dr P R Montgomery
Elastoma Intrapapillare Perforans (Miescher) Dr O L S Scott
Mixed Salivary-type Tumour of Skin with Malignant Recurrence Dr D E Sharvill

Meeting May 18 1961

Case for Diagnosis ? Eruptive Melanomata
A W McKenzie MRCP (for H J Wallace FRCP)

M N, female, aged 25. Nursery attendant
History: Two years ago this patient noted the appearance of a non-pruritic nodular eruption on the buttocks and arms. New lesions had continued to appear, with the probable disappearance of others. General health was good, with no other specific symptoms.
On examination: Reddish-brown nodular lesions, some with superficial scaling, were present on the buttocks and arms. Lichenoid lesions were also present on both forearms. General physical examination, full blood count and X-ray of chest were normal.
Comment: Clinically, the diagnosis was thought to be either the *lentiginose profuse* of Brocq (1921), or the group recently described by Sanderson (1960) – eruptive telangiectatic cellular nævi.

Biopsy in 1959 showed the histology of a cellular nævus with junctional activity, while another in 1960 showed a picture of malignant melanoma. It was difficult to reconcile the apparent benign clinical picture with the florid histology of malignancy.

REFERENCES
Sanderson K V (1960) *Brit. J. Derm.* **72**, 302
Brocq L (1921) Précis – Atlas de Pratique Dermatologique. Paris; p 1048

Dr H Haber: This patient shows a continuous eruption of tumours which from the histological point of view show characteristic features of malignant melanoma. There is segregation of nævus cells at the epidermodermal junction with invasion of both the epidermis and the underlying cutis. There is also a considerable inflammatory reaction demonstrable. Without knowing the history of the case one has to make a diagnosis of malignant melanoma in every specimen. Multifocal melanomata are known and not unusual. The history of the case, however, shows that the lesions behave clinically at least for the present as perfectly benign. Juvenile melanoma in an adult has, therefore, to be considered. This lesion as described by Spitz (1951) shows a typical histology. The chief characteristics are verrucous epidermal hyperplasia with segregation of bizarre nævus cells and Sophie Spitz giant cells. There is also œdema of the corium with maximal dilatation of vessels. Inflammation and mitotic figures complete the picture. This classical histology is unfortunately not found in every case, otherwise the diagnosis would be easy. In my experience there are cases of juvenile melanomata which are very difficult to distinguish from true malignant melanomata. In cases like this one has to consider the age of the patient first to make a diagnosis of juvenile melanoma. Even so, the patient has to be put under long surveillance as only the clinical course of each individual is able to provide a positive answer to such a difficult problem.

REFERENCE Spitz S (1951) *Amer. J. Path.* **24**, 591

Dr H J Wallace: Some of these melanomata have evolved from the smaller lichenoid lesions.

Dr G A Beck: Should one advise this patient against pregnancy?

Professor C D Calnan: I think it is conceded now that pregnancy does not have the adverse influence on malignant melanomata that was previously supposed (George, Fortner & Pack, 1960, *Cancer* **13**, 854).

***Trichophyton rubrum* Infection with Griseofulvin Intolerance**
Suzanne Alexander MB (for H R Vickers MD FRCP)

S O, aged 22, female, research student
History: First noticed discoloration of toe-nails in May 1959, and of left finger-nail in July 1959. Seen in the out-patient clinic of the Radcliffe Infirmary in November 1959 when all the toe-nails and the left middle finger-nail were found to be infected with *Trichophyton rubrum*. Griseofulvin 1 g daily was given from November 13 to November 23 1959, when she was admitted to hospital with malaise and diarrhœa and found to have a generalized pink macular rash, splenomegaly and hepatomegaly. Griseofulvin was stopped immediately on admission, the diarrhœa subsided within twenty-four hours; the rash faded after four days, and she left hospital on the eleventh day. Since then, she has remained fairly well, except for recurrent attacks of 'chilblains' on the hands, even in warm weather, and a marked recurrence of the *Trichophyton rubrum* infection of the nails, which had apparently cleared after the griseofulvin. One month ago, a circinate pink rash developed on the dorsum of her hands.
Past history: Chickenpox; measles; tonsillectomy; carbuncle on arm, 1954, treated with penicillin; Herpes zoster, 1958. Has had chilblains 'for years'. She used to get them badly on feet and mildly on hands, but latterly she has had them more on hands, and her feet have been relatively clear.
Family history: Parents both alive. Mother has 'heart disease'. No family history of *Trichophyton rubrum* infection, but several uncles and her grandfather worked in mines and patient has stayed with them.
Clinical findings: Finger and toe nails are thickened and white. The hands are cold and show 'chilblain circulation', and there is a diffuse reticulated macular rash on the dorsum of the hands. Spleen just palpable. General examination otherwise normal.
Investigations: Hb and R.B.C. normal during the whole period of observation. W.B.C. persistently low – average 3,000 (polys. 2,000). Platelets, reticulocytes, and film normal. No L.E. cells found on repeated examination. W.R. and Kahn negative. Coombs test negative. E.S.R. persistently

raised (40 mm in one hour in January 1960 to 20 mm in one hour at present) (Westergren). Serum proteins: Total 8·4, albumin 5·0 g/100 ml. Plasma electrophoresis shows some increase in γ-globulin. Bone marrow examination normal. Urine normal.

A complement-fixing antibody to griseofulvin, of the incomplete type (as shown by Coombs test), and present in the γ-globulin fraction of the serum has been found.

A positive Prausnitz-Küstner reaction was obtained in a volunteer on intradermal injection of the patient's serum, followed by intradermal injection of griseofulvin four days later. Transfer of passive cutaneous anaphylaxis to two guinea pigs was unsuccessful.

Skin biopsy from finger: Chronic non-specific dermatitis.

Comment: This girl was treated with griseofulvin in November 1959 and developed a sensitization reaction ten days later, consisting of a pink morbilliform rash, a fever of 102·8° F and hepatosplenomegaly. All these subsided quite quickly, but she has since then had a persistently raised E.S.R. and changes on her hands which, at one time, were thought to be those of periarteritis nodosa. L.E. cells have never been found and her general health is fairly good. Skin biopsy from lesions of the hands was not suggestive of lupus erythematosus. The patient was anxious to have a further course of griseofulvin, but we felt this would be unwise. Because of the possibility of sensitivity to griseofulvin, a search for antibody was made: her serum was found to contain a complement-fixing antibody to griseofulvin, and this was shown to be in the γ-globulin fraction of the serum by testing the various fractions of the serum obtained by electrophoresis in agar. This antibody did not act as a precipitin, and Ouchterlony plates were negative. Nor did it give direct agglutination with red cells which had been incubated with griseofulvin, but it was of the incomplete type and could be demonstrated by the indirect Coombs test using griseofulvin-treated cells. It appeared to be specific as there was no complement fixation with penicillin (which she had had in the past), streptomycin or tetracycline, or with normal skin or warts. There was, however, complement fixation with an extract of white blood cells and with D.N.A., and these findings are quite common in collagen diseases. The sera of twelve other patients treated with griseofulvin were tested and did not contain an antibody to this drug, but a similar antibody was found in the serum of a 64-year-old farmer who had a 'light sensitivity' rash seven days after taking griseofulvin. He too complained of dizziness and malaise, but his rash very much resembled discoid L.E. It subsided within a week of stopping the drug. The serum of neither patient was tested at the height of the reaction; both sera were found to contain this antibody one year afterwards.

The histories in both cases are suggestive of a causal relationship between griseofulvin and the sensitization reaction.

Dr H R Vickers: I first saw this patient in November 1959 at the height of the reaction when she developed the rash. The rash started on the hands and feet and spread centrally in the course of twenty-four hours. Apart from having chilblains she had had no real trouble with her skin previously, and had been quite healthy. After discharge from hospital she went to Cornwall for the Christmas holiday, and when we saw her in January she had other lesions on the back of the fingers and toes. These were raised, rather hard papules, and Dr Alexander wondered then whether she was developing polyarteritis nodosa.

The lupus erythematosus-like appearance of the skin has only appeared within the last few weeks; she at first had a little atrophy but it is much more like lupus erythematosus than it was some time ago. The scraping from the skin did show *Trichophyton rubrum* but it does not necessarily mean that the skin change now seen is due to *Trichophyton rubrum* infection. She is anxious to get rid of it and wants us to give her more griseofulvin but we feel that we may precipitate disseminated lupus erythematosus or one of the related auto-immune reactions.

Is it safe to give her griseofulvin and remove her nails, at the same time giving her steroids to counteract the lupus erythematosus effects? My own view is that one should not do anything potentially toxic, particularly in a young patient.

Dr A J E Barlow: The original case I described (Barlow *et al.* 1959) twice developed a marked leucopenia after taking the drug but on the third occasion the drug was given without any significant alteration in the blood count. Another man developed an erythema of his face on two occasions after taking griseofulvin and stopped the drug of his own accord. I have never seen anyone who has developed a lupus erythematosus pattern of reaction to griseofulvin and from the history the two would definitely seem to be associated. The fact that her complement is still fixed by griseofulvin would, I think, make further administration of the drug extremely dangerous.

REFERENCE Barlow A J E, Chataway F W, Hargreaves G K & La Touche C J (1959) *Brit. med. J.* ii, 1141

Dr A Jarrett: This may well be a primary collagen disease of the lupus erythematosus type, and it is well known that these patients react abnormally to drugs. In this case the drug happens to be griseofulvin.

Dr P D Samman: I have one patient who presents a very similar picture to this; he has a very severe epilepsy which is controlled by anti-epileptic drugs and has patches on the fingers almost identical with this. When we started griseofulvin it upset him completely, and he became so severely epileptic that we withdrew the drug. The erythema was present before the drug was given.

Dr Brian Russell: The patient has 'liver palms', and I wonder if a disturbance of liver function is the background to this toxic effect.

The President: She was on very small doses, 1 g per day for ten days.

Idiopathic Hyperlipæmia with Glycosuria
E Wilson Jones MRCP and F Ray Bettley FRCP

H J, female, aged 40. Service manageress.
History: Eight weeks ago she developed a scattered papular eruption on the trunk and limbs, the individual lesions gradually increasing in size and number.
Past history: Twelve months ago developed a fleeting arthritis which involved several joints, and was associated with iritis and conjunctivitis of the left eye. She was investigated in hospital and was found to have a glycosuria, which disappeared with a 1,500 calorie diet; the joints cleared up and a tentative diagnosis of Reiter's syndrome was made. Since that time the patient has complained of intermittent thirst and polyuria, and also a loss of 2 stone in weight.
On examination: Skin: Numerous small xanthomatous papules with a tendency to grouping on the limbs and trunk. The papules have an erythematous margin and vary in size from 1 to 4 mm in diameter. There are a few lesions on the palms and soles, but there is no diffuse involvement of the creases. No xanthelasma.
General examination: A fit-looking, overweight patient (13 st. 8 lb). No lymphadenopathy or hepatosplenomegaly. Cardiovascular system normal. Blood pressure 145/90. No fundal hyperlipæmia observed.
Investigations: Urine strongly positive for sugar. Glucose tolerance curve: Fasting level 219, maximum 394 (at one and a half hours), falling to 250 mg/100 ml in three hours. Total lipid 5·5 g/100 ml (normal range 0·36–0·82 g/100 ml). Cholesterol 512 mg/100 ml. Fæcal trypsin normal. Serum lipoproteins raised. Serum proteins within normal limits. Liver function tests, electrolytes and blood urea normal. Insulin tolerance test: normal insulin sensitivity. ECG normal. Blood count: no significant abnormalities.
Progress: The patient was placed on a 1,000 calorie diet, and within one week the serum had lost its turbidity, and her glycosuria had nearly been eliminated. Fasting blood sugar had fallen to 132 mg/100 ml.
Comment: This is a case of idiopathic hyperglycæmia in which glycosuria is an unimportant concomitant. This condition is distinct from the hyperlipæmia which may occur in ketotic patients, with severe, untreated diabetes.

The following cases were also shown:

(1) Cat Scratch Disease (2) Eruptive Angiomata
Dr A W McKenzie (for Dr H J Wallace)
Erythrokeratodermia Variabilis Dr G C Wells
Necrobiotic Nodules of Knees
Dr M A Smith (for Dr H J Wallace)
Case for Diagnosis: ? Hyalinosis Cutis et Mucosæ
Dr P F D Naylor (for Dr H J Wallace)
Porokeratosis of Mibelli
Dr H W Buck (for Dr E W Prosser Thomas)
(1) ? Pili Torti (Mother) (2) Pili Torti (Child)
Dr R R M Harman
Mycosis Fungoides treated with Cytotoxic Drugs
Dr B H Bass (for Dr Brian Russell)
Case for Diagnosis: Papules on Neck consisting of Clumps of Elastic Fibres, with Erythema
Dr E Lipman Cohen
? Tylosis Dr B Bentley Phillips

Meeting June 15 1961

Lymphocytoma and Lymphosarcoma
J S Pegum MRCP

R H, female, aged 82
History: In 1924 'yellow translucent nodules' appeared on the forehead. Since then she has had many similar lesions on the forehead, temples, eyebrows and cheeks. In the summer there are exacerbations presumably due to sunlight. She was previously shown at this Section as a case of lymphocytoma (Pegum 1954). In 1960 she developed a large lump on the left temple, which was diagnosed as lymphosarcoma.
On examination (May 1961): On the left temple there is a collection of translucent papules. Elsewhere on the forehead and temples can be seen scars, the result of former treatments with radium and carbon dioxide snow. On the left cheek there is an area of erythema.
Investigations: Biopsies in 1940 and 1954 showed lymphocytoma, with lymphocytes and reticulum cells in the dermis. The biopsy of 1960 shows a lymphosarcoma, with lymphocytes and lymphoblasts.
Treatment: The lymphocytoma has been treated with radium, carbon dioxide, X-rays and thorium-X. The lymphosarcoma was treated with X-rays (220 kV, 1 mm Al, 0·5 mm Cu, 250 r × 10) and showed an excellent response (Dr Walter Shanks).

When this patient was shown here in 1954 the point was made that lymphocytoma was a very benign condition and that she had had it for thirty years and no harm had come of it. It was not until last year, thirty-six years after the onset of the condition, that harm did come of it when suddenly a lymphosarcoma appeared and grew with alarming rapidity.

REFERENCE Pegum J S (1954) *Proc. R. Soc. Med.* **47**, 1061

Ehlers-Danlos Syndrome Associated with Streptococcal Hypersensitivity

G M Cochrane MB (for D I Williams FRCP)

M M, female, aged 36. Housewife

History: She was well until end of January 1961 when she had acute inflammation of the right ankle for forty-eight hours followed by effusions in both knees and similar transitory acute arthritis of the left ankle. Treated with Disprin gr 60 daily for three weeks.

On admission 1.3.61: Temperature 100° F; pulse regular 105; œdema of both legs; œdema of right thigh with raised erythematous area and bulla at centre; red tender nodule on left elbow; slight effusion left knee. Fever continued over the next three weeks and she lost 12 lb in weight. Extensive œdematous red lesions developed over the buttocks, with blistering followed by ulceration. With change of position similar lesions appeared at sites of pressure.

25.3.61: Bilateral pleural effusions; in all 50 oz were aspirated from right and 55 oz from left pleural cavity. Pericardial rub heard. Œdema of both legs, slight proteinuria and hypoalbuminuria.

Prednisone 60 mg daily, chlorothiazide 1 g b.d. on three days a week and high protein diet given; œdema disappeared, plasma proteins returned towards normal, general condition improved and weight was regained. Reduction of prednisone to 20 mg daily was followed within seventy-two hours by localized œdema of vulva and right side of face. On prednisone 60 mg daily fresh lesions continue. There seem to be five stages in their natural history: (1) *In dependent* areas local œdema, pitting on pressure. (2) After two to three days: tender, red, raised patches. (3) In some lesions there have been bullæ, which frequently burst leaving moist red bases unless secondarily infected. (4) Over the next ten days lesions become dusky, in parts yellowish and with resolution of œdema striæ distensæ. (5) Within three weeks lesion flat, striated with telangiectasia.

Investigations: Hb 85% (12·6 g/100 ml). W.B.C. 11,000 (neutros. 8,250, lymphos. 2,310, monos. 440, eosinos. 0). E.S.R. 22 mm in one hour (Wintrobe); has fallen to 2 mm in one hour. Throat swab: Group A hæmolytic streptococci. Anti-streptolysin 'O' titre: 2.3.61, 480 units; 13.5.61, 820 units; 10.6.61, 495 units.

Fig 1

Urine protein 60 mg/100 ml. No proteinuria during past ten weeks.

Plasma proteins: Total 5·1 g/100 ml. Albumin 23%, α_1 6·5%, α_2 27%, β 14·3%, γ 29·2%. Repeated estimations show change to normal electrophoretic pattern, 29.5.61. Pleural fluid: Numerous pus cells; protein 5 g/100 ml.; culture – no growth; polys. 80%; lymphos. 20%. Chest X-ray (23.3.61): Bilateral pleural effusion. C reactive protein, Rose Waaler, L.E. cells, blood cultures, antinuclear factor, liver function tests, serum transaminase, serum cholesterol, glucose tolerance curve, serum uric acid, blood urea, W.R. and ECG were all normal.

Biopsy of skin lesion shows moderate hyperkeratosis. Some of the cells of the epidermis show hydropic degeneration and in some areas there is keratic plugging. The dermis is patchily infiltrated with chronic inflammatory cells mainly centred around the skin appendages which also show considerable surrounding fibrosis. There is no abnormality of blood vessels. There is fragmentation and degeneration of elastic tissue elements.

Biopsy of unaffected skin: Elastic tissue appears abnormal, being increased in amount and clumped into small aggregates.

Comment: This has seemed to us an unusual disease, beginning with acute arthritis and associated with fever, loss of weight, abnormal plasma protein pattern, with increase in α_2 and γ fractions and low albumin, œdema, pleural effusions and skin lesions, some of which finally look like necrobiosis lipoidica.

The absence of L.E. cells, the poor response to prednisone in a dose below 60 mg daily, and the absence of antinuclear factor in the serum make systemic lupus erythematosus unlikely. Polyarteritis nodosa has not been evident in the skin biopsies, the patient is normotensive and there is no eosinophilia. It may be significant that the antistreptolysin titre was high at 480 units, and rose to 820 units, and has now fallen to 495 units.

The lesions seem to be related to local pressure. When she sat in bed they appeared over the buttocks, elbows, and shoulders. She was nursed on her side and developed similar lesions over her hips. When lying prone she developed œdema over the sternum, supraclavicular triangles, abdomen, right breast, and right side of the face – the side on which she preferred to lie most of the time. Fig 1 shows the large baggy swelling below her chin – developed in a dependent area. At first there was local œdema, which in distensible areas was considerable, and after two to three days there was a raised red centre. Fig 1 is a later stage showing a very œdematous area which is resolving; the striæ distensæ and telangiectasia may be seen. Finally the lesion becomes flat after three or four weeks, and the skin appears atrophic.

Dr T M L Price: This seems to be a systemic disorder though her general health has been surprisingly good except when she had pleural effusions. I doubt if steroid therapy explains her healthy appearance.

The lesions look quite different according to whether the skin breaks down or not, and whether scarring occurs; I think they are different in kind as well as varying in severity. The first manifestation of most of the lesions, however, is a collection of subcutaneous fluid, and this seems to damage the skin. The lesions usually appear in dependent areas and are more severe when subjected to pressure.

Apart from the diagnostic problem, suggestions about treatment would be appreciated. The illness is of long standing and causes considerable distress, particularly in view of her good general health.

Dr H Haber: I believe this patient has an Ehlers-Danlos syndrome with angioneurotic œdema.

Dr I B Sneddon: I think this is a combination of the Ehlers-Danlos syndrome and urticaria. It would be worth trying antihistamines in a high dose to see if the swellings can be suppressed. I have seen penicillin urticaria in a known case of Ehlers-Danlos syndrome where the clinical picture was very similar to the present case and the weals and swellings lasted many weeks. This diagnosis would not explain the attack of pleurisy.

The President: Did your patient's condition clear up with antihistamine?

Dr I B Sneddon: My patient did clear up with antihistamines but the duration of individual lesions was far longer than usual and she had the same pendulous swelling of the neck.

The President: I think most people would agree that this patient had early manifestations of Ehlers-Danlos syndrome.

Dr D I Williams: I saw this patient a few weeks ago and thought she had a very curious condition. I am not sure that since that time I have advanced any further towards a diagnosis. The suggestion that she has Ehlers-Danlos syndrome with some other disease superimposed is interesting, although I find it hard to believe. Certainly the histology would support the suggestion. Dr Sneddon seems to be the only Member who has seen anything resembling this case, and his patient had urticaria. To try antihistamines would seem to me to be sense, although the corticosteroids work more dramatically in cases of urticaria than has happened here. I can make no intelligent suggestion of a diagnosis to include the bizarre skin lesions, very painful joints and the pleural effusion. There is no evidence to clinch a diagnosis of vasculitis. The streptolysin titre is very high, and it is tempting to believe that this is a curious reaction to the streptococcus or its products.

POSTSCRIPT (19.10.61): Following Dr Sneddon's suggestion, since May 19, 1961, she has been treated with chlorpheniramine maleate 16 mg daily and prednisone was gradually withdrawn. No further lesions appeared. She was discharged on July 7, 1961, and remains well. – G M C

The following cases were also shown:

(1) Epiloia
(2) Inveterate Papular Urticaria
Dr Brian Russell

(1) Urticaria Pigmentosa with Bone Changes
(2) Smokers' Keratosis
(3) Lichen Nitidus
(4) Linear Eruption
Dr J S Pegum

Livedo Reticularis (Primary)
Dr P M Deville

Subacute Systemic Lupus Erythematosus: Porphyria
Dr C F H Vickers (for Dr I B Sneddon)

Reticular Livedo with Cerebrovascular Lesions
Dr R E Church

Kyrle's Disease
Dr H M Drummond (for Dr C M Ridley)

Book reviews

Textbook of Medical Treatment
edited by
Sir Derrick Dunlop BA MD FRCPEd FRCPLond
Sir Stanley Davidson BA MD Hon MD(Oslo) FRCPEd FRCPLond
and S Alstead CBE MD FRCPEd FRCPLond FRFPS
8th ed pp xix+983 60s
Edinburgh & London: E & S Livingstone 1961

The introduction to this book points out with truth that most textbooks of general medicine have not the space to give a complete account of treatment, and weaken their scanty advice with vague statements such as: 'vaccines may be of value' or 'a well-balanced diet should be given'.

This books sets out to remedy these defects by providing such complete and explicit directions that even an inexperienced doctor will find all he needs to know about the management of his patients. An admirable aim, and where it is achieved an admirable book. However, the standards vary as much as the authors, of whom there are more than twenty. Random sampling of the book over widely divergent subjects shows that few of the authors manage to confine themselves to describing only those treatments that really work.

Too often does the reader bump against pieces of dead wood or mumpsimus of just that kind criticized in the introduction: 'measures recommended by our forefathers continue to be included in spite of the fact that some of them have been shown to be useless'. For instance, in the treatment of enuresis: (pp 284–5) 'The general health must be seen to . . . enlarged tonsils and adenoids may require removal . . the child must have a rest in the middle of the day . . . the bedclothes must not be too heavy' and so on. Similar things are said about asthma: (p 724) 'Infection of the nasal sinuses must always be looked for . . . climatic conditions are believed to play an important part . . . flatulent dyspepsia and constipation should be treated'. As Walshe wrote of similar statements made about the treatment of disseminated sclerosis 'to assume that such matters bear any relation to the disease is a travesty of reasoning which should not have survived the discipline of a scientific education'.

Tedious ineffectualities like these cover the essential things which get interred with them. Much traditional nonsense is harmless, and some of it is even helpful as a placebo for the patient, or a cover for ignorance for the doctor; but it is disturbing to find traditional matter that is dangerous being repeated in this book. Here is the treatment of shock after heavy blood loss (p 454): 'He should be immediately placed in bed between blankets . . . the body heat should be restored by placing hot water bottles along both sides of the body, due care being taken not to burn the patient . . . when available a radiant heat cradle should be used, as a more even warming of the body can be obtained without the danger of burning the patient'.

The body heat has never been lost, so why restore it? Passing urine never cools anybody, so why should losing blood? The shocked patient wishes to be cool. He needs to be cool. Cold helps him to conserve the blood from surface vessels to make more available for the heart and brain. 'The shocked man spends his dying strength trying to throw off the blankets and shock-producing cradles which are heaped upon him by well meaning but ignorant bystanders' – Sir Heneage Ogilvie.

Though marred by these imperfections the book is rich with the experience of many distinguished physicians and will continue to be a valuable work of reference for many practitioners and students. Stanley Alstead's contribution on 'The Care of Old People' is outstandingly informed and practical; all sorts of sensible things are there: if an old person has had a symptomless scirrhous carcinoma of the breast for years, but has come to hospital because of her stiff knees, then the diagnosis is 'stiff knees'. Treat old folk at home whenever possible. Make them *do* something, whether it be playing bowls or going to church. See their rugs do not slip on polished floors and arrange hand rails to help them get about. Those are the kind of down-to-earth practical things that only a few of the authors mention. For instance in the ear, nose and throat section, the treatment of nose bleeding described by the late Wilfred Trotter is not mentioned. He pointed out that nose bleeding usually stops if the patient is given ¼ gr of morphia and propped up in bed with the head turned sideways, a cork between the teeth and a towel on the shoulder to bleed into, and left in peace. Could not this be tried before the douching followed by packing under local anæsthetic recommended here? Also is it not safer to remove foreign bodies from children's noses with a blunt hook rather than forceps because an object slippery with mucus may be shot further up the nose?

The great size of the book is rather a disadvantage (it runs to nearly a thousand pages) and it could be greatly improved by ruthless pruning; but superfluities cannot usually be excised without offending the superfluator, and so it would

need the temperament of the Miller of the Dee as well as the energy of Hercules to carry out this work, for most contributors are hospital colleagues or close friends of the editors. Among the ballast that would be better overboard are the paragraphs written at the start of a subject, before the author's mental wheels have properly got going. During this literary warming up even the best mental machines turn out heavy pieces of scrap. Here is Professor Alstead getting started on 'The Management of Old People in Hospital':

'The function of the hospital in relation to the elderly infirm cannot be discussed fully here. There is however a growing realization of the need for a positive and constructive policy to deal with the disabilities of old people, and a wider appreciation of some of the difficulties of medical practice among patients who no longer enjoy a sense of security within the social structure of the community. Such considerations have also profoundly affected current medical and administrative policy . . .' &c, &c.

Overboard please!

Here is another bit of old iron, worked in the traditional pattern – the opening paragraph of the section on migraine (p 873):

'In the management of migraine it is important that the patient should guard against precipitating causes of an attack if they are known. Any error in refraction should be corrected; over-fatigue (physical and nervous) and indiscretions of diet should be avoided; disease of the accessory nasal sinuses should be treated; if there is a history of dyspepsia and flatulence the gall bladder should be investigated, and if the gall bladder is diseased, appropriate treatment should be arranged.'

From what Kipling called 'all the obese unchallenged old things that stifle and overlie us' . . . Good Lord Deliver Us!

Immunopathologie in Klinik und Forschung und das Problem der Autoantikörper
edited by Prof Dr P Miescher and Prof Dr K O Vorlaender
2nd ed pp xvi+694 illustrated DM 90
Stuttgart: Georg Thieme 1961

The appearance of the second and enlarged edition of this book so soon after the first is testimony to its usefulness for clinicians and immunologists. It covers a field of medicine which is growing rapidly in interest, mainly because of increasing evidence for the participation of immunological mechanisms in the pathogenesis of various common inflammatory diseases. In its wide coverage of both clinical and experimental observations, this volume has no counterpart in English, and it will probably remain for some years to come as the most extensive single source of information on the possible association of auto-antibodies with human diseases.

The present edition is the combined work of 23 collaborators, though the two editors, Miescher and Vorlaender, have taken a disproportionately large share in the preparation of the text. It begins with a brief but masterly survey of the principles of modern immunology by Grabar. But the two main sections of the book are those on immunohæmatology and on the immunopathology of various inflammatory organ diseases of man and their possible replication in experimental animals. In the former, not only are the relevant varieties of hæmolytic anæmia fully treated, but long subsections also deal with the various forms of immunologically-induced leucopenia and thrombocytopenia. In the latter section are considered *seriatim* the possible participation of auto-antibodies in the pathogenesis of certain diseases of the thyroid gland, the kidneys, the eye and the liver, as well as present views on the possible allergic element in rheumatism, lupus erythematosus, encephalomyelitis, diabetes and silicosis. The volume ends with a short survey of modern views on the reactions induced by the transplantation of tissues and organs.

As is to be expected from these distinguished collaborators, this volume is a fine compendium of present-day ideas in immunopathology. That this edition has been substantially revised and enlarged can be seen from its greater length, newly-added contributors, and the many additional references (now happily set out with the full title of the paper added) in the extensive bibliographies which follow each chapter.

Protein Biosynthesis
A symposium held at Wassenaar, August 29 – September 2, 1960, under the auspices of UNESCO and the Council for International Organizations of Medical Sciences
edited by R J C Harris
pp xii+409 illustrated 95s
London: Academic Press 1961

The introduction of new techniques invariably leads to almost explosive outbursts of research in many subjects. This has been particularly true of protein biochemistry during the past few years. The use of the electron microscope together with the development of procedures for the fractionation of subcellular components has focused attention on the possible sites of protein synthesis in the cell. The refinement of chromatographic methods for the separation of amino acids and peptides and the availability of radioactively labelled metabolic intermediates has stimulated numerous studies on the mechanism of protein biosynthesis. Scientists trained in many different

disciplines have been involved and their results are scattered amongst a variety of journals. The present volume contains 20 main papers together with 6 additional short communications given by principal workers in the field at a recent international symposium.

Several of the contributions make it clear that although the microsomal fraction, which forms the endoplasmic reticulum in the whole cell, is an important site of protein formation, other organelles, such as the nuclei and mitochondria, can also synthesize proteins. The basic technology of protein synthesis appears to be the same for each site but it is emphasized that there may be several types of protein formation. Thus, some proteins are made for export and excreted by the cells that made them, some are made for temporary use and are later destroyed, and some are made as permanent cellular constituents during growth and multiplication. There are also many intriguing problems, e.g., although liver microsomes make immunologically active serum albumin, the ribosomes extracted from them make protein material, but not recognizable serum albumin.

Concepts of Medicine
edited by Brandon Lush MD MRCP
pp x+286 illustrated 50s
Oxford, &c: Pergamon Press 1961

Dr Lush has collected 26 papers that have interested him and which had been previously published in medical journals covering the three themes, concepts of medicine, of health and disease and of medical research. The authors are nearly all physicians of the utmost fame. It is presumably to that journal's credit, and not a mark of narrow reading by Dr Lush, that 15 of the papers are reprinted from the *Lancet*. They make excellent reading but the regular reader of the *Lancet* may find nearly 5s each rather a high price to pay for the papers he has not already got.

The Chemistry of Immunity in Health and Disease
by David W Talmage MD and John R Cann PhD
American Lecture Series No. 407
pp xi+178 illustrated 46s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

This book is one of a series of 'American Lectures in Living Chemistry' conceived, so the foreword tells us, by Dr I N Kugelmass and the publisher 'to advance our knowledge of chemical medicine in the cause of clinical practice'. Dr Kugelmass explains his concept by writing 'Once chemical truths, proofs and convictions become sound foundations for clinical phenomena, key hybrid investigators clarify the bewildering panorama of biochemical progress for application in everyday practice, stimulation of experimental research, and extension of postgraduate instruction. Each of our monographs thus unravels the chemical mechanisms and clinical management of many diseases that have remained relatively static in the minds of medical men for three thousand years. Our new Series is charged with the *nisus élan* of chemical wisdom supreme in choice of international authors, optimal in standards of chemical scholarship, provocative in imagination for experimental research, comprehensive in discussions of scientific medicine, and authoritative in chemical perspectives of human disorders.'

Naturally such a foreword – apart from our ignorance of *nisus élan* – fills us with great expectations, particularly as both authors have worked in the field of immunology, but it must be confessed that the book itself is a sad disappointment. It is a review of current immunology, in which the subject matter is not very well arranged and in which the controversial points are treated very superficially. It seldom deals with problems of immunity in relation to human disease, or the metabolic influence of antigen-antibody reactions on living cells. There is a need for a book with the title that the authors have adopted, but this is not the book.

Scientific Aspects of Neurology
Leeds Neurological Sciences Colloquium 1959–60
edited by Hugh Garland TD MD FRCP
pp xi+264 illustrated 50s
Edinburgh & London: E & S Livingstone 1961

The editor and the Leeds Medical School are to be congratulated on these lectures delivered a year ago by twenty men on a wide range of topics to which no single author could possibly have done equal credit. The majority are review articles of complex and controversial subjects. The high standard of criticism achieved by Walshe on the pyramidal system is not so evident in Jefferson's article on sleep which contains yet another reproduction of Magoun's sheaves of arrows arising in the reticular formation. Exley ably discusses the inchoate pharmacology of this most fashionable resort in the central nervous system. The demyelinating disorders are reviewed by van Bogaert, H G Miller and Lumsden, with agreeably incompatible conclusions.

The 'handmaidens' of neurology are well represented by an outstanding article by Denis Hill on the EEG focus, and the clinical sections include a masterly account of the treatment of trigeminal neuralgia by Pennybacker.

McKissock's 'The Treatment of Posterior Communicating Aneurysms' struck your reviewer as unfortunate for the very reason of its authoritative conclusion that carotid ligation is the treatment of choice, as, despite the title, the series

appears to have included an unspecified number of internal carotid aneurysms. Moreover, to assert that a controlled trial is 'ethically proper' without any mention of consultation with the patient merely stresses the need for discussion of the ethics of clinical trials.

Textbook of Clinical Medicine
edited by John W Todd
pp xi+564 illustrated £5 5s
London: Pitman 1961

The appearance of a new textbook of medicine is an interesting event. Dr Todd's book is a composite text with ten authors, evenly divided between teaching and non-teaching hospitals.

The editor has written several sections himself, including the forthright opening pages in which many cherished beliefs are challenged in pungent style. The student is made to think of the purpose of his diagnostic effort and is reminded that a clever diagnosis that turns out later to be correct may nevertheless be wrong if founded on inadequate data at a time when no certain diagnosis can be made.

It is always easy to criticize style, content and presentation in a composite textbook and this one is no exception. The general level is very simple and, although this is to be commended, there are some parts in which the information is frankly inadequate for the modern student. Although attractively produced and easy to read one doubts whether this book will offer a serious challenge to the established British textbooks for undergraduates, which are, incidentally, appreciably cheaper.

Art and the Scientist
by Geoffrey Lapage MA MSC MD MINSTBIOL
pp xii+115 illustrated 42s
Bristol: John Wright 1961

Here is a book about the drawings and paintings that have been used to illustrate scientific writings. This is a difficult enough subject to present, since it is specifically not concerned with works of graphic art which some men of science have produced, nor with the work of artists who have illustrated the work that scientists have done, nor again is it intended to be in any sense a history of the illustrations of scientific works. Its purpose is 'to consider the characteristic qualities of drawings and paintings done by scientific men and also certain questions raised by these', and (as can be guessed by this quotation) its style is apt to be a little gluey; so that this reviewer longed for some clear pattern or sequence or unifying generalizations to help him through the 106 pages in which these qualities are patiently analysed.

But if the text is rather heavy going, the illustrations are a delight. They are beautifully reproduced, and cover the whole panorama of scientific writing from Leonardo to our near-contemporaries, with drawings from Cheselden and Hooke, from the diaries of Scott's Antarctic expedition, and from artists like Stubbs, highlighting this variegated path; and the subjects range from bestiary to histology, from a very knobbly and archaic 'evolutionary tree' to the almost indecently clear drawings of Gray's Anatomy, and from wistful flower-paintings to the unromantic 'innards' of the lug-worm.

Within its limited intentions this book is unique. One has no doubt that it is comprehensive and scholarly, even without the evidence of its formidable bibliography. And if, to the superficial reader, its arguments sometimes seem overcomplex and its conclusions elusive, the determined student of these marches of art and science will surely be rewarded.

Advances in Thyroid Research
Transactions of the Fourth International Goitre Conference, London, July 1960
general editor Rosalind Pitt-Rivers
pp xix+537 illustrated £6 6s
Oxford &c: Pergamon Press 1961

This book constitutes one of the most important contributions to thyroid literature in recent years. All the papers read at the Fourth International Goitre Conference have been published, after careful editing, and illustrated with a useful selection of charts and diagrams. Since some 600 endocrinologists from 50 countries attended the Conference the scope of the work can be realized and in this volume will be found contributions to every aspect of this rapidly expanding field of research which embraces not only endocrinology but also many aspects of biochemistry, genetics, geophysics and experimental biology.

The volume is especially valuable in that the references are to be found at the end of each paper and it is surprising that such a well-edited and beautifully printed book could have been produced so rapidly after the Conference. This is an essential reference volume for all medical libraries.

Das Menschliche Knochenmark: Anatomie, Physiologie und Pathologie nach Ergebnissen der intravitalen Markpunktion
by Prof Dr med Karl Rohr
3rd ed pp xvi+593 illustrated DM 98
Stuttgart: Georg Thieme 1960

This third edition of Rohr's pioneer volume on the human bone marrow follows in the path of the previous two. There is, of course, new information based on phase contrast and electron microscopy and introduction of isotopes has given a better insight into the launching and life span of

the blood cells. However, the special character of this book lies in the co-ordination of the biology of the blood with general basic pathology. Development, Mature Existence, Decline, Inflammation and Neoplasia are still the same as they were in 1939 when Rohr, a pupil of Naegeli, published this work on hæmatology which, unlike the usual textbooks, is not centred on the peripheral blood cells but on the blood-forming tissues themselves. This is not an easy book to read but, while it demands concentrated study, it will reward those who make the effort. The illustrations, diagrams, index and collection of references are all up to the previous standard.

Neural Mechanisms of the Auditory and Vestibular Systems
edited by Grant L Rasmussen PHD and William F Windle PHD SCD
pp xiv+422 illustrated £6 6s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961
The papers presented at this Symposium, held in June 1959 and organized by the U.S. Institutes of Health, comprise a series of up-to-date pronouncements, faultlessly reproduced, by some of the world's foremost authorities upon a number of basic problems, anatomical and physiological, of the mammalian cochlear and vestibular systems.

Of special interest are the contributions by von Békésy and Hallowell Davis upon the mechanical system and electrophysiology of the cochlea; by Engström and Wersall upon the electron microscopy of the cochlear and vestibular sense organs; by Brodal and Gernandt upon the anatomy and electrophysiology of the vestibular neural pathways; by Rasmussen and Gacek upon the efferent fibres in the cochlear and vestibular nerves, and by Neff upon the role of the auditory cortex in sound discrimination. No efforts have been spared by the organizers of this Symposium and the results, so well presented in this volume, should earn them the thanks and deep interest of all who find themselves concerned with the urgent and absorbing problems of the VIII nerve system.

Essentials of Neurology
by John N Walton MD MRCP
pp xvii+442 illustrated 30s
London: Pitman 1961
This textbook of neurology has been written primarily for senior students and practitioners and it should be of real value to them. The treatment of the subject is orthodox, excellent clinical descriptions well integrated with anatomy, physiology and biochemistry, and a short but adequate account of the morbid anatomy of the diseases described. There are two criticisms to make; too many rare neurological disorders are mentioned in passing without adequate description and the short chapter on 'disorders of the mind' might with advantage be altered in the next edition. It is of very little value to discuss the affective disorders, schizophrenia and the psychoneuroses in a few pages of a textbook of neurology and the space might be better employed in a further account of the psychiatric aspects of organic neurological disease. These, however, are minor criticisms of a first-class book, well written, well produced and reasonably priced.

Praktische Hämatologie
by Prof Dr H Begemann and Dr H-G Harwerth
pp xii+298 illustrated DM 33
Stuttgart: Georg Thieme 1961
This book is unlikely to be useful in the English-speaking world. It is unbalanced, as much space being devoted to sideroblastic anæmias as to iron deficiency; it is inadequate, as for example when it dismisses acute leukæmia in childhood in the phrase 'it occurs in all age groups and is even not uncommon in children' and fails to discuss the pathogenetic mechanism of pernicious anæmia; it is even wrong, as when it states that the mortality of hæmolytic transfusion reactions is about 50%, and that the treatment of choice is immediate exchange transfusion.

Multiple Sclerosis: Prognosis and Treatment
by Leo Alexander MD, Austin W Berkeley PHD and Alene M Alexander
pp xii+188 illustrated 60s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961
Quantification of the infinitely variable clinical phenomena of multiple sclerosis presents formidable problems. Dr Leo Alexander of the Boston State Hospital is one of the few who have attempted their solution. The present book describes studies carried out on these lines during more than a decade. The numerical scoring of disability at periodic re-examinations has been subjected to statistical analysis in an attempt to establish patterns of natural history, to clarify prognosis and to evaluate a variety of treatments. Such work is laborious, fraught with uncertainties, and traditionally occupies a lowly place in the hierarchy of scientific investigation. It has the enormous advantage that it deals at first hand with a specifically human disease and not with its intriguing but questionable analogues in the experimental animal. As an essay in the establishment of some kind of measurement in a very confused field of natural phenomena it is courageous and not entirely unsuccessful.

The book will fascinate every worker in this special field, and should be read by all physicians with an interest in diseases of the nervous system.

At the pragmatic level Dr Alexander's demonstration of the value of ACTH in active cases and acute episodes of multiple sclerosis is supported by current experience in Great Britain – but why should prednisone be apparently less effective? Although the theoretical basis of the therapy is obscure, claims that the course of the disease may be favourably influenced by repeated small blood transfusions have been supported by a number of reputable European neurologists, amongst whom Schaltenbrand is conspicuous. The present author furnishes statistical evidence in this connexion which is at least suggestive and certainly justifies further investigation.

Sometimes the clinical data seem to be carrying more weight of statistical analysis and interpretation than they can comfortably bear, but in general this is a most praiseworthy effort to bring order out of chaos and one of the most important contributions to the clinical literature of the disease for many years.

An Atlas of Pain Patterns
by Lucian A Smith MD MS(Med)
Norman A Christensen MD MS(Med)
Norbert O Hanson MD
Donald E Ralston MD MS(Med)
Richard W P Achor MD MS(Med)
Kenneth G Berge MD MS(Med)
George W Morrow Jr MD MS(Med)
and Arthur H Bulbulian MS DDS FACD
pp x+54 illustrated £5
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961
This beautifully produced book, from a group of clinicians at the Mayo Clinic, analyses the pain patterns created by some of the commoner upper abdominal lesions. This is done by means of a brief introductory chapter, followed by a handsome atlas of coloured diagrams of the pathological anatomy of hiatus hernia, of peptic ulceration and of biliary and pancreatic disease.

Any book which presents a lucid interpretation of such an important subject as upper abdominal pain is to be welcomed. Unfortunately the price for this slim volume of 54 pages will put it beyond the pocket of many readers. They would, however, pass a most profitable hour in perusing this book in the library.

A Primer of Electrocardiography
by George E Burch MD FACP and
Travis Winsor MD FACP
4th ed pp 293 illustrated 37s 6d
London: Henry Kimpton 1960
This well-established book on clinical electrocardiography has, throughout three previous editions, been recognized as one of the best introductions to the subject. It is clearly written and the diagrams are very good. Minor revisions have been made for the present edition; the application of vectorcardiography to the clearer understanding of electrocardiography is considered, but since substantial advance has been made in this field during recent years a fuller presentation of this aspect would be welcome and we hope the editors will expand their book in the next edition.

System of Ophthalmology
Vol II The Anatomy of the Visual System
by Sir Stewart Duke-Elder GCVO FRS and
Kenneth C Wybar BSC MD ChM FRCS
pp xxii+901 illustrated 130s
London: Henry Kimpton 1961
The publication of 'The Anatomy of the Visual System' by Sir Stewart Duke-Elder and Kenneth C Wybar is an epoch-making event in ophthalmic literature. Sir Stewart, in the first edition of his 'Textbook of Ophthalmology', produced a section on anatomy of first-class reference value. The new book is of much greater bulk owing to the fact that anatomy to-day is in no sense a dead subject but is rapidly growing. Considerable attention has been paid to the historical development of the subject. In addition stress is laid on the advances made in the anatomy of the visual system in the last thirty years. It is only quite recently that the detailed structure of the angle of the anterior chamber of the eye has been intensively investigated. The finer ramifications of the intraocular vascular system are only now becoming appreciated. The introduction of the electron microscope and its application to ocular anatomy in the last twenty years has effected a revolution in our appreciation of ocular structure. The book is fascinating and anyone picking it up cannot fail to browse happily among its contents, particularly the brilliant thumb-nail vignettes of the great anatomical discoverers. There is an excellent section on the neurology of the visual system. Altogether the book is one which must find a place in the library of every ophthalmologist.

Sex Differentiation and Development
Proceedings of a Symposium held in London
on April 10 and 11 1958
Memoir No 7. edited on behalf of the Society for
Endocrinology by C R Austin
pp x+198 illustrated 45s
London: Cambridge University Press 1960
All the memoirs published by the Society for Endocrinology have been excellent and this, the seventh, on sex differentiation is no exception. The papers here collected were given at a Symposium planned in a most ambitious way. The subjects dealt with ranged from sex determination in the honey bee and the vexed problem of queen bee substance, through current methods

of chromosome counting and nuclear sexing of cells and polymorphs, to the origin and development of oocytes and such broader subjects as sexual behaviour in mammals. There is a splendid thumbnail sketch of sexuality in bacteria and a very full discussion of the problems involved in Turner's and Klinefelter's syndromes. The book has excellent references and is an essential reference work in this new and rapidly expanding field.

Textbook of Medicine
edited by Sir John Conybeare KBE MC DM FRCP and W N Mann MD FRCP
13th ed pp xvi+987 illustrated 45s
Edinburgh & London: E & S Livingstone 1961

This well-established and popular textbook of medicine has now reached its 32nd year and its thirteenth edition. These figures alone prove it to meet the requirements of medical students. It is of traditional design, relatively small and provides the reader with the basic information he requires. But in spite of its many excellent features it is perhaps beginning to show signs of its age. It is probably impossible to revise sections which have been written many years ago in such a way that they regain a contemporary flavour. This weakness is highlighted by a completely new section on kidney disease written for this edition by Professor Rosenheim: it is succinct, authoritative and up to date. By contrast a number of other contributions seem a little outmoded. Chronic bronchitis, a common and important disease, is allotted only 2 pages while bronchiectasis, which is now relatively rare, receives 6. The section on blood diseases does not accurately reflect modern hæmatological thought.

These are minor criticisms of emphasis and approach; they can be applied with some justice to all textbooks which have passed through more than one or two editions. For the rest 'Conybeare', as it has long been known, deserves nothing but praise. The articles are clear; all the facts are to be found within its covers; the radiographs are well-reproduced and informative; and the tables of normal values and body measurements are most useful. There can be no doubt that it will continue to enjoy its well-deserved popularity with students of medicine.

An Atlas of Dental and Oral Radiology
by Sydney Blackman MRCS LRCP DMRE(Camb)
pp xi+371 illustrated 84s
Bristol: John Wright 1959

This volume is essentially an atlas of radiographs illustrating the normal anatomy and the various pathological conditions met with in the teeth and jaws and their associated structures. The radiographs reproduced are of a high standard and reflect the mastery of technique which the author has attained. The publishers deserve great credit for the clarity of the reproductions, for the large clear print and for the spacious lay-out.

The text is the weak part of the book; maybe too brief for proper understanding and accuracy. Some of the terminology, such as 'apical hæmatoma' and the classification of the disturbances of bone growth tend to conflict with modern teaching.

This atlas should be used as an adjunct to illustrate the accepted textbooks on oral pathology more fully.

Orthopædics
by George Perkins MC MCh FRCS
pp xiii+975 illustrated £6 6s
London: The Athlone Press (University of London) 1961

There are too few textbooks of orthopædics by English master surgeons. Since Robert Jones published the first in 1923 we have seen but two, those by Walter Mercer and Philip Wiles. Elmslie, Lambrinudi, Trethowan, Bristowe, and now Fairbank, have all died before they could find time to produce a volume of their experience, although of course their original publications were many and authoritative.

Perkins suggests that the writing of a book on orthopædic surgery after retirement from practice might seem the height of folly, but this is just the time to write and to the blissfully ignorant such wisdom is not folly. The book may well be full of fads and fancies, it may be didactic, and it cannot help, nor should it try to avoid, being dogmatic, because it sums up the deductions of a lifetime spent in practical work in orthopædics and in active and stimulating argument with colleagues and friends. Dogma is never invariably acceptable and, as Perkins suggests, many orthopædic surgeons will disagree with some of his views, but so many, including this reviewer, will be left with the feeling that perhaps Perkins is right!

The arrangement and descriptions are essentially clinical; pathology, symptoms and management are combined in a manner which instils information at once and without having to read through several different sections to obtain the complete picture. In this his arrangement of the book in sections on bone and individual joints, followed by the spine, the neck, the nerves and the muscular tissues is amply justified. This is a textbook of orthopædics rather than a symposium of the disorders of the locomotor system, so it is perhaps disappointing that there are no chapters on the general principles of treatment of deformity and no description of the important adjuvant techniques of appliance-making, physiotherapy or

the use of plaster of Paris, but perhaps these things are better learned by experience than by reading.

There is no difficulty in enjoying the book: the production is excellent, the illustrations clear, and the style so readable that the burden of study is light. Perhaps not the book for the student in the last throes of pre-examination swotting, but essential for the orthopædic house surgeon and registrar, and a useful reference for the consultant who wishes to think again about some of his stereotyped practices.

This is a personal book and, like its author, will always command respect.

Pregnancy and Diabetes Mellitus
by Lars Hagbard MD
American Lecture Series No. 449
pp viii+101 illustrated 54s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

Professor Hagbard from Gothenburg has analysed 554 diabetic pregnancies, the majority at different hospitals in Sweden. The material has been very carefully and critically examined and the conclusions are compared with those of other workers whose results have been reported in the literature, which is widely quoted. Hagbard advocates, as others do, the strictest control of the diabetes during pregnancy, admission to hospital well before term and delivery in the 37th or 38th week. More than half of his cases are delivered vaginally.

It is a pity that the circulation of this valuable review is likely to be restricted by its price. The book contains 85 pages and there are no plates, yet it costs £2 14s 0d. Can the publishers, or their English representatives, not explain why the volumes of the American Lecture Series cost about three times as much as seems reasonable?

A Course in Epidemiology
edited by I I Elkin
translated from the Russian by C R Pringle PHD
pp vii+518 illustrated 70s
Oxford &c: Pergamon Press 1961

The Pergamon Press is to be congratulated in general on its initiative in translating Soviet medical textbooks and it has started biased in favour of this book, but it was difficult to find anything deserving favourable comment. It is disappointing, but not surprising, that epidemiology in the U.S.S.R. is interpreted as being restricted to the study of infectious diseases. It is depressing to find it inadequate for this limited field.

In the historical section Koch rates a photograph, but is only mentioned in the text because he attacked Mechnikov. No British epidemiologist is mentioned in this section, but bourgeois epidemiology in general is attacked, chiefly on the grounds that in the West insufficient weight has been given to the importance of social conditions in relation to diseases.

In no section are there any definitions of mortality rate, incidence or prevalence, nor is there any discussion of methods of measuring them or their possible errors. There is the usual unwillingness to give 'basic' figures when referring to the U.S.S.R. in recent times; relative figures are usually given. Most of the figures cited refer to countries outside the U.S.S.R. before 1953. There are no references to source material to justify the numerous dogmatic statements. There is no evidence that statistics has made any impact on epidemiology in the U.S.S.R.

The section on tuberculosis rates only 7 pages out of 507. In it there are three tables of mortality and incidence, none refer to the U.S.S.R., and nearly half are pre-1932. There is no mention of the discovery of a specific therapy nor any discussion of its epidemiological consequences; nor is there any reference to controlled trials.

My impression is that the U.S.S.R. is in urgent need of a Bradford Hill.

The Chemical Basis of Clinical Psychiatry
by A Hoffer MD and Humphry Osmond MRCS DPM
American Lecture Series No. 402
pp xvi+277 68s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1960

This book is mainly a review of the evidence derived from the authors' own experimental work for the hypotheses that adrenaline and its derivatives have an important role in the ætiology of anxiety, depression, and schizophrenia. However, there is a lack of confirmatory evidence for these hypotheses outside the authors' own laboratory, and the present volume does little to restore confidence. For example, conclusions have apparently been drawn from a very small number of cases, sometimes from only one, and a statistical evaluation of results is missing. The book cannot be recommended as presenting an objective view of the role of adrenaline in mental illness.

The Reluctant Surgeon
by John Kobler
pp 359 21s
London &c: Heinemann 1960

This is the English edition of an American work on John Hunter, primarily intended for non-medical readers. It is a pleasantly written, full account of Hunter's life, a little embroidered here and there, but accurate and with a comprehensive bibliography. This book is likely to find a wide public, both outside as well as inside the medical profession.

The Surgical Treatment of Intracranial Meningiomas
by Collin S MacCarty BA MD MS
pp viii+69 illustrated 36s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961
The author describes the techniques he favours in dealing with intracranial meningiomata at their various sites. He considers that to reduce the risk of post-operative bleeding temporary complete excision of the bone and dural flap is desirable at some stage of the operation upon these tumours. Consequently he does not limit himself to scalp flaps and considers that an undulating S-shaped incision which facilitates retraction to expose a wide area of skull has considerable advantages in some situations. Post-operatively dural closure is not completed and the scalp incision is closed with a single layer of sutures. Illustrative examples of operations upon meningiomata in various situations are described.

This monograph is well produced and illustrated. The case histories provided are so incomplete as to have little value and the description of the operations is too superficial to be of value to neurological surgeons – for whom the publication is no doubt intended.

Biological Approaches to Cancer Chemotherapy
A Symposium held at Louvain, June 1960 under the auspices of UNESCO and the World Health Organization
edited by R J C Harris
pp x+431 illustrated 96s
London: Academic Press 1961
All who are in any way interested in the chemotherapy of neoplastic diseases are aware that the main factor against success in treatment is the lack of *specific* toxicity of the agents at present available. The need is for compounds with increased selectivity for tumours; and translated from the clinical to the experimental sphere, the immediate question is how information now (or potentially) available about the properties of living cells may be used in drug design. This excellent book brings together contributions to a symposium held last year in Louvain to consider this problem.

From even the present knowledge of cells an enormous range of approaches to tumour control is available. Eminent authorities from a wide variety of disciplines, and drawn both from Europe (including the U.S.S.R.) and the U.S.A., explored aspects ranging from a general cell theory and 'feedback mechanism' in biological synthesis, to immunological studies, virology and hormonal growth control. Professor Danielli's thesis – that the selectivity of a drug for one cell lineage can be enhanced by increasing the number of cell variables on which the action depends – has already been confirmed experimentally, and it introduces the whole symposium on an optimistic note. Modifications in action may be introduced at a bewildering number of biochemical levels. Since tumours of similar histology may differ by tenfold in their content of a given enzyme, matching of drug to tumour may involve specialized examination of neoplastic tissue, a novel extension of the uses of biopsy. The incorporation of radioactive tritium (^3H), with its extremely localized β-irradiation, may be a further means of confining the noxious effects to the tumour cells. The benefit from radiomimetic agents is often limited by the effect on the bone marrow, and interesting suggestions are made for its protection. If each contributor to this valuable symposium has but left his particular door a little ajar, the brief glimpses of what may be possible in cancer chemotherapy are undoubtedly entrancing.

Tools of Biological Research
edited by
Hedley J B Atkins DM MCh FRCSEng HonFACS
pp xii+155 illustrated 37s 6d
Oxford: Blackwell Scientific Publications 1961
The third and last volume of this outstanding series is considerably slimmer than the two which preceded it. The choice of subjects is again excellent and includes such topical techniques as chromosome analysis, autoradiography and infrared spectrophotometry. References are given in full at the end of each chapter and the standard of editing and printing is excellent.

Regional Block
by Daniel C Moore MD
3rd ed pp xvi+393 illustrated £5
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961
Books about local analgesia tend to fall into two categories – either they are long, heavy and exhaustive or short, portable but sketchy. Dr Moore has compromised by limiting himself to the subject of regional block and describing only one technique for each procedure. Thus the book is relatively short but extremely useful, particularly to resident medical officers and general practitioners.

The text is easy to read and well illustrated. Many of the drawings are the work of that accomplished artist and surgeon, Donald L Curtis, who is a colleague of the author. The subject matter is well organized and classified while the index is an object lesson in thoroughness.

It is refreshing to find an author laying so much stress on the disadvantages, contra-indications and complications of various methods, for instance, the oft-repeated warning that adrenaline added to local analgesic solutions injected around the base of a digit will almost certainly lead to

gangrene or that local analgesia for operations on the penis carries the risk of causing impotence. The only complication not mentioned is the danger of damage to the spinal roots when indwelling catheters are extracted at the end of continuous subarachnoid block (spinal analgesia) – a complication which caused this method to be given up in the United Kingdom even before certain legal decisions regrettably made it too hazardous for anæsthetists to use either form of spinal analgesia. However, this is the only omission in an otherwise well-written and excellently produced book.

The Scientific Basis of Medicine
Annual Reviews 1961
British Postgraduate Medical Federation
pp xi+342 illustrated 40s
University of London: The Athlone Press 1961
This is another of the volumes containing 'Lectures on the Scientific Basis of Medicine', which have previously been printed by the Athlone Press. These are university lectures given in London each year and have rightly attracted much attention. The new title of this volume has been chosen to try and give a more accurate description of what is to be found in these lectures and thus make them more generally available. This volume is as good as any of its predecessors and is an essential for every medical library.

A Symposium on pH and Blood Gas Measurement: Methods and Interpretation
edited by Ronald F Woolmer VRD BA BM FFA RCS
pp. viii+210 illustrated 30s
London: Churchill 1959
The average clinician has usually been out of touch with laboratory techniques for so long that he is unable to challenge either the method or the accuracy of the measurements he asks for. It is refreshing, therefore, to find a group of physiologists, biochemists, physicists and electronic experts meeting a number of anæsthetists, physicians, surgeons and the representatives of laboratory instrument manufacturers to discuss more accurate methods of estimating pH and blood gas measurements. This gathering was made possible by the kindness of the Ciba Foundation and met under the able chairmanship of Professor Ronald F Woolmer, Director of the Anæsthetic Research Department of the Royal College of Surgeons of England. A considerable amount of information is presented which, although primarily of interest to research and laboratory workers, can also profitably be read by practising anæsthetists, physicians and surgeons. The presence of scientific observers from the leading laboratory equipment manufacturers was particularly fortunate as already an instrument has been marketed which makes possible the rapid estimation of pH or pCO_2 from blood samples. The book is well produced, easy to read and has delightfully clear photographs and diagrams.

The Treatment of Hypertension
by Sir George White Pickering MA MD FRCP FRS
William Ian Cranston MD MRCP
and Michael Andrew Pears MD MRCP
pp xi+175 illustrated 56s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961
The purpose of this book is to place before the practitioner and the consultant physician the treatment of hypertension by the various methods which are available at the present time. This purpose is admirably achieved.

The early chapters set the scene by discussing with commendable brevity the nature of hypertension and the assessment of its treatment, before turning to the details of the different ways by which the blood pressure can be effectively lowered. Naturally the main bulk of the book is concerned with the various drugs which can be used, their modes of action, methods of administration and side effects. An eclectic attitude has been taken, and little space has been expended on those drugs which are no longer in general use, or which are not recognized by the authors. But even here they make a point, and in so doing will please their readers by such sentences as 'This state of affairs seems to us to be a classic illustration of the chaos to which applied therapeutics can be reduced by the uncritical acceptance of hypotheses and the failure to control clinical observations'.

This book combines clarity concerning the details of treatment with a thought-provoking and scientific mode of presentation, and is in itself an example of the way in which medical practice is developing. Quite apart from its value in the practical management of patients, it is full of interest and should have a wide appeal.

Diagnosis in Locomotor Disorders
by Kenneth Stone DM (Oxon) MRCP
pp 224 illustrated 25s
London: Oxford University Press 1960
The purpose of this short volume is to provide practitioners with a quick reference book, the subject matter being confined to essentials. Signs and symptoms occurring in disorders of the locomotor system are set out alphabetically. Beginning thus with 'Aching, generalized', 'Atrophy, muscular', the author goes on in serial fashion to end with 'Paræsthesia', 'Polyarthritis' and 'Spasticity'. Should the reader not be able readily to find what he wants, he can resort to the index. Over fifty illustrations and a number of tables still further clarify the text.